UNIVERSITY OF COPENHAGEN
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# PhD Thesis

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# Withdrawing from antidepressants

## Evidence for guideline recommendations and consideration of biological and psychological effects

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***To the patients***

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## Preface

This thesis is a synopsis based on the following three articles:

1. **Sørensen A**, Ruhé HG, Munkholm, K. The relationship between dose and serotonin transporter occupancy of antidepressants – a systematic review. *Published, Molecular Psychiatry, 21 September 2021.*
   DOI: 10.1038/s41380-021-01285-w
   Protocol: https://osf.io/2f7k5/?view_only=cb987f4a428c4d369b34926b132382c8

2. **Sørensen A**, Jørgensen KJ, Munkholm, K. Clinical practice guideline recommendations on tapering and discontinuing antidepressants for depression: a systematic review.
   *Published, Therapeutic Advances in Psychopharmacology, 11 February 2022.*
   DOI: 10.1177/20451253211067656
   Protocol:
   https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=220682

3. **Sørensen A,** Moncrieff J. The psychology of psychiatric drug action – a narrative review of psychiatric drugs as emotion regulation strategies. *Submitted, 2022.*

All studies in this PhD thesis were conducted at and funded by the Nordic Cochrane Centre.

### The origin of this project

As a psychology student and research assistant on a clinical trial of Emotion Regulation Therapy at Aarhus University, I learned that what we do as psychologists is help our patients regulate their difficult and painful emotions better. I was taught the science behind what clinical psychology had established as a maladaptive emotion regulation style (e.g., avoidance, suppression, worrying, rumination, substance use), which causes and maintains psychopathology, and how to help our patients change to an adaptive emotion regulation style (e.g., acceptance, problem solving, emotional tolerance, cognitive defusion) through psychotherapy.

Meanwhile, having written my bachelor's thesis on *the implications of epigenetics on the rationale for psychiatric drug treatment*, I was aware of the empirical challenges facing the medical model of psychiatric drug action. I noticed how our textbooks in biological psychiatry were allowed to make the exact mistake we had just been taught in research methodology never to make – confusing correlation with causation – when using correlative brain scan studies as evidence that mental illnesses are biological disease that drugs can fix.

I remember thinking *'what, then, do psychiatric drugs do?'* and started conceptualizing them as an emotion regulation strategy with respect to their psychoactive effects of reducing emotional intensity, reducing arousal, dampening excessive thought activity, inducing sedation, etc.

My next thought was that if psychotherapy helps patients to not avoid and suppress their painful emotions, but to experience them, act on them, and gain executive self-control over them, then what is the difference between using psychotherapy to treat psychopathology and to help patients come off psychiatric drugs when that time comes?

This became the subject of my master's thesis (and of course, there are major differences), however, no one at Aarhus University were able to supervise me on the matter. I therefore contacted Peter Gøtzsche for some informal advice. He replied. We met the following month and he offered me the opportunity to proceed with my ideas on psychiatric drug withdrawal as a PhD project at the Nordic Cochrane Centre once I graduated as a psychologist later that year.

This PhD thesis has changed fundamentally since then, but it would not have come to be if it weren't for that meeting and series of events.

## Acknowledgements

Peter C. Gøtzsche deserves my deepest gratitude for giving me the opportunity to do a PhD based on just a brief meeting an early Monday morning. Thank you for always being there, always believing in me, and for having created the Nordic Cochrane Centre – an outstanding, active, and ever inspiring research environment to be part of as long as it was.

Thanks to my colleagues Asger, Dina, Kristine, Kim, Lars, and Marie who I'm all sincerely sad I didn't get to know better (this time!). Good luck to Asger in our next minigolf tournament – *du har en revanche til gode*. I would like to thank Frihild and Jannie for, without a single exception, always being there to help us PhD students with practicalities and for always smiling and spreading joy. It means more than you know.

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I would like to thank psychiatrist Lisbeth Kortegaard. You took the time to listen and support me when no one but me thought it was a good idea for a psychologist to take up hardcore biological psychiatry matters. Thanks for introducing me to the critical psychiatry network in Denmark back in 2014 which helped me through my bachelor's thesis, my master's thesis, and now through my PhD. You invited me into the community, and for that I am you forever grateful.

A special thanks also to my former clinical supervisor and mentor at Aarhus University, Mia Skytte O'Toole. You invited me to join your outstanding research on Emotion Regulation Therapy which was what sparked my ideas of investigating the psychologist's role in psychiatric drug withdrawal, which ultimately lead me to this PhD.

Thanks to Birgit Toft, Olga Runciman, Jørn Ditlev Eriksen, Bertel Rüdinger, Mark Horowitz, Michael Hengartner, and Laura Delano for numerous and invaluable conversations on psychiatric drug withdrawal. Thanks to Benjamin Jensen for being Benjamin Jensen – you've helped me through the final year of my PhD more than you know.

## English summary

Withdrawal symptoms and various psychological challenges can occur upon discontinuing or reducing the dose of antidepressants, potentially preventing the patients from coming off their antidepressants or making it very difficult. With as widely used a drug as antidepressants, how to minimize and overcome withdrawal-related issues should be both empirically investigated and covered in the clinical practice guidelines. Care must be taken not to confound withdrawal symptoms with relapse when concluding on the effect and necessity of the antidepressant upon discontinuation.

In this thesis I investigated the relationship between antidepressant dose and serotonin transporter (SERT) occupancy, the primary biological effect of most antidepressants, which is likely involved in the mechanism behind antidepressant withdrawal symptoms (article 1); to what extent and of what quality clinical practice guidelines (CPGs) on depression provide guidance on tapering and discontinuation of antidepressants (article 2); and whether psychiatric drugs can be conceptualized as an emotion regulation strategy, focusing on their psychoactive and psychological effects in a drug-centred model, and what implications that may have for the treatment rationale and withdrawal (article 3).

Article 1: We found that SERT occupancy increased rapidly in the lower dose range and reached a plateau at around 80-85% at a dose corresponding to the minimum effective dose of all the 10 antidepressants we reviewed. This hyperbolic dose/occupancy relationship appeared to follow the Michaelis-Menten equation and may explain the limited clinical effect of dose escalation and the potential occurrence of withdrawal symptoms even at small dose reductions in the lower dose range.

Article 2: Of the 21 CPGs we included, 15 (71%) recommended to discontinue antidepressants by slowly or gradually reducing the dose; 15 (71%) informed that withdrawal symptoms can occur; and 17 (81%) recommended to continue antidepressant treatment after symptomatic remission for a certain period of time. No guidance was provided on dose reductions, how to distinguish between withdrawal symptoms and relapse, psychological challenges, or generally on how to help patients get through withdrawal. The guidance was generally scarce and vague, guideline quality was low, and the discontinuation phase of treatment was not included in any of the treatment algorithms or flow charts.

Article 3: In a drug-centred model, what psychiatric drugs do fit the definition of emotion regulation, providing an alternative to the medical model of psychiatric drug action. We argued that psychopharmacology and psychotherapy target psychopathology at two different levels which may conflict with each other. Long-term psychiatric drug treatment, while reducing symptoms, may have negative psychological effects that constitute maladaptive emotion regulation by confirming metacognitive beliefs and emotional schemes of uncontrollability, durability, and incomprehensibility. Suggesting these effects as the main mechanism of action of psychiatric drugs has implications for the treatment rationale and for the potential issues arising when coming off psychiatric drugs.

In conclusion, how to avoid, minimize, and help patients get through antidepressant withdrawal symptoms is insufficiently covered in clinical practice guidelines. The linear tapering regimens recommended in the guidelines are likely at high risk of causing withdrawal symptoms which were not distinguished from relapse. It thus remains unknown how many patients in remission can stop their antidepressant without relapsing and, conversely, how many patients that genuinely benefit from maintenance treatment, as those that succeed may, to some degree, be those who were not prone to withdrawal symptoms. To solve this problem, occupancy studies may theoretically inform a pharmacologically rational tapering regimen by identifying the doses corresponding to a gradual and slow-enough unblocking of the target receptors, potentially resulting in mitigation of withdrawal symptoms. Following the non-linear dose/occupancy relationship, a hyperbolic dose reduction regimen appears necessary to secure a linear and gradual reduction in occupancy, which would require performing multiple dose reductions below half of the lowest standard available doses. Whether hyperbolic tapering mitigates the risk of withdrawal symptoms compared with linear tapering cannot be concluded from these data and must be investigated in clinical research. In general, more RCTs comparing different tapering regimens and supportive interventions are needed. Finally, psychological challenges were not addressed in the guidelines, including potential issues related to the fading of the drugs' psychoactive effects upon discontinuation, which can be conceptualized using the psychological concept of emotion regulation.

## Resumé (Danish summary)

Abstinenser og forskellige psykologiske udfordringer kan opstå ved udtrapning af antidepressiva, hvilket potentielt kan forhindre patienterne i at komme ud af medicinen eller gøre udtrapningen meget svær. Med så udbredt et lægemiddel som antidepressiva bør det undersøges empirisk og beskrives i kliniske retningslinjer, hvordan man minimerer og overkommer udtrapningsproblematikkerne. Det er vigtigt ikke at forveksle abstinenssymptomer med tilbagefald, når man ved seponering vil konkludere, om medicinen er effektiv og nødvendig.

I denne afhandling undersøgte jeg forholdet mellem dosis af antidepressiva og receptormætning af serotonintransporteren (SERT), som er den primære biologiske effekt af de fleste antidepressive lægemidler, og som formentlig er en del af mekanismen bag abstinenssymptomerne (artikel 1); omfanget og kvaliteten af vejledning om udtrapning og seponering af antidepressiva i de kliniske retningslinjer for depressionsbehandling (artikel 2); og om psykiatriske lægemidler generelt kan konceptualiseres som emotionsreguleringsstrategier med hensyn til deres psykoaktive og psykologiske effekter i en *stof-centreret* model, samt hvilke konsekvenser dette kan have for behandling of udtrapning (artikel 3).

Artikel 1: Vi fandt, at receptormætningen af SERT steg kraftigt i det lavere dosisinterval og nåede et plateau ved omkring 80-85% ved en dosis svarende til den mindste effektive dosis for alle de 10 præparater, vi inkluderede. Dette hyperbolske forhold mellem dosis og receptormætning syntes at følge Michaelis-Menten-ligningen og kan formentlig forklare den begrænsede kliniske effekt af dosisøgning og forekomsten af abstinenssymptomer selv ved små dosisreduktioner i det lavere dosisinterval.

Artikel 2: Af de 21 kliniske retningslinjer, vi inkluderede, anbefalede 15 (71%) at seponere antidepressiva gennem langsomme eller gradvise dosisreduktioner; 15 (71%) informerede om, at abstinenssymptomer kan forekomme og 17 (81%) anbefalede at fortsætte antidepressiv behandling i en bestemt periode efter remission. Der var ingen vejledning om dosisreduktioner, hvordan man skelner mellem abstinenssymptomer og tilbagefald, psykologiske udfordringer eller generelt om, hvordan man hjælper patienter med at komme igennem abstinenserne. Vejledningen var generelt sparsom og uklar, kvaliteten af retningslinjerne var lav og udtrapningsfasen af den antidepressive behandling var ikke inkluderet i nogen af behandlingsalgoritmerne eller flowdiagrammer.

Artikel 3: Ud fra en *stof-centreret* model kan virkningen af psykiatriske lægemidler beskrives som emotionsregulering, hvilket giver et alternativ til den medicinske model for virkemekanismerne ved psykofarmaka. Vi argumenterede for, at psykofarmakologi og psykoterapi behandler psykisk lidelse på to forskellige niveauer, som kan være i konflikt med hinanden. Langtidsbehandling med psykofarmaka kan – samtidig med at det reducerer symptomer – have

negative psykologiske effekter, der udgør en uhensigtsmæssig emotionsregulering ved at bekræfte metakognitive overbevisninger og emotionelle skemaer om ukontrollerbarhed, varighed og uforståelighed. Disse effekter kan have betydning for både behandlingsrationalet og for eventuelle udfordringer i forbindelse med udtrapning.

Vi konkluderede således, at det er utilstrækkeligt beskrevet i de kliniske retningslinjer, hvordan man undgår eller minimerer abstinenser samt hvordan man hjælper mennesker igennem dem. Den lineære udtrapning, som både blev brugt i undersøgelserne og anbefalet i retningslinjerne indebærer formentlig en stor risiko for at forårsage abstinenssymptomer, som ikke blev skelnet fra tilbagefald i hverken forskningen eller retningslinjerne. Det er således stadig ukendt, hvor mange patienter i remission, der kan stoppe deres antidepressive behandling uden tilbagefald; og omvendt, hvor mange patienter, der oprigtigt har gavn af deres vedligeholdelsesbehandling, eftersom dem, udtrapning lykkedes for, kan være dem, der ikke får abstinenser. Receptormætningsstudier kan formentlig bidrage til at løse dette problem ved at kortlægge de doser, der udgør en farmakologisk rationel udtrapningsplan med en gradvis og tilstrækkeligt langsom nedgang i receptormætningen, hvilket potentielt kan nedsætte risikoen for abstinenser. Taget det ikke-lineære forhold mellem dosis og receptormætning i betragtning er hyperbolsk udtrapning af dosis formentlig nødvendigt for at sikre en lineær og gradvis nedgang i receptormætning, og det kræver, at man reducerer dosis i mindre dele end standarddoserne tillader, selv efter halvdelen af den mindste producerede standarddosis. Hvorvidt hyperbolsk udtrapning mindsker risikoen for abstinenser sammenlignet med lineær udtrapning kan ikke konkluderes fra disse data, da det kræver klinisk forskning. Der er generelt behov for flere randomiserede undersøgelser, som sammenligner forskellige udtrapningsmetoder og interventioner. Afslutningsvist fandt vi, at psykologiske udfordringer ikke blev adresseret i retningslinjerne, herunder potentielle udfordringer i forbindelse med aftagningen af lægemidlernes psykoaktive effekter ved udtrapning, hvilket kan konceptualiseres som emotionsregulering.

# Introduction

## Withdrawal symptoms

Withdrawal symptoms have been reported for all antidepressants[1–3] since the advent of the first tricyclics in the 1950's.[4,5] While academia only recently started prioritizing this issue, patients have long organized themselves in peer-support networks aimed at helping each other overcome the struggles of psychiatric drug withdrawal.[6–8]

For antidepressants, there are now three systematic reviews on withdrawal symptoms;[9–11] one systematic review on the incidence, severity, and duration of withdrawal symptoms;[12] two systematic reviews on interventions for discontinuing antidepressants;[13,14] one systematic review on the barriers and facilitators of antidepressant withdrawal;[15] and several ongoing clinical trials.[16,17]

Withdrawal symptoms include affective, somatic, sensory, cognitive, gastrointestinal, sleep disruption, and disequilibrium symptoms,[9–11] which may occur upon stopping or reducing the antidepressant dose.[1,12,18,19] The average incidence rate is 51% of the patients as identified in RCTs and 57% when combining survey studies, naturalistic studies, and RCTs.[12] Half of the patients rate the symptoms as severe.[12] We previously found some preliminary evidence of a relationship between duration of antidepressant use and incidence rate of withdrawal symptoms, which increased from about 25% after three months to about 40% after 12 months for SSRIs; and from about one third after three months to half of the patients after 12 months for paroxetine specifically.[20] The reported duration of withdrawal symptoms ranges from days over weeks to months and, in rare cases, even years;[12] and we previously found that protracted withdrawal symptoms are not uncommonly expressed among patients on online forums.[21]

Withdrawal symptoms pose an inherent problem when concluding on the effect and necessity of a drug in a patient upon discontinuation, because potential symptoms of withdrawal and relapse – two fundamentally different clinical situations – overlap to some degree. This introduces a confound to understanding and treating deterioration occurring upon stopping or reducing the drug, both in research and clinical practice. It is therefore crucial to minimize (or avoid) the risk of withdrawal symptoms, to give the symptoms sufficient time to pass before concluding that a relapse occurred, and to help patients get through the difficult period.

## Potential mechanisms involved in antidepressant withdrawal symptoms

There is no unequivocal theory or evidence why antidepressant withdrawal symptoms occur. Withdrawal symptoms in general, however, are theorized to arise when the body detects a reduction in available ligand compared with the altered homeostatic setpoint caused by

continuous administration of a substance.[22–26] Gradual and small dose reductions ('tapering') will thus reduce the magnitude of this disequilibrium while progressing towards cessation of the drug, resulting theoretically in less withdrawal symptoms compared with larger dose reductions or abrupt discontinuation.

Following this general theory, determining the optimal dose reduction regimen requires knowledge on the degree to which the different doses reach their target receptors (measured as receptor occupancy via PET and SPECT techniques), which is the pharmacologically rational unit to taper according to, rather than the dose in mg *per se*. This is theoretically relevant for tapering and have been hypothesized,[19,27] because the change in available ligand that the body reacts to occurs when the targeted receptors are 'unblocked' upon dose reduction.

Most antidepressants have primary affinity for the serotonin transporter (SERT),[28,29] which functions to reuptake serotonin from the synapse. Blocking SERT is thus one way to pharmacologically affect and change the synaptic serotonin levels. However, as no chemical imbalances in neurotransmission have been consistently identified in depression, this pharmacological effect may act as a perturbation rather than a correction. As a fundamentally homeostatic biological system, the nervous system does not accept perturbations, but eventually start counteracting and adapting to them, for example by downregulating postsynaptic receptors.[22,30,31] This likely decreases the sensitivity to the now elevated level of neurotransmitters, thus reestablishing equilibrium at a new homeostatic setpoint that is dependent on continuous intake of the same drug and dose.

When the dose is reduced, the homeostatic mechanisms kick in and start adapting to the now reduced neurotransmitter levels compared with the adaptations that occurred as response to the continuous drug-intake (according to general principles of homeostasis). This may potentially activate an underlying withdrawal state, lasting theoretically until equilibrium has been re-established. Withdrawal symptoms are therefore temporary in nature and provide no indication of the patient's clinical condition, which is why they need to be distinguished from relapse and treated accordingly.

**Psychological challenges and barriers to coming off antidepressants**

Patients also report various psychological challenges when attempting antidepressant withdrawal, including anxiety, uncertainty, worry of relapse, insufficient emotion regulation skills, perceived etiology of depression being biochemical, and need for social support.[15,32–37] Psychosocial support or intervention that target these issues may thus be relevant during tapering.

Furthermore, little attention has been paid to the psychoactive and psychological effects of psychiatric drugs in general, including whether these effects introduce issues when

coming off the drug. Qualitative studies into the subjective experience of these effects, and of taking antidepressants in general, are scarce. In some of the few and small existing studies, patients for example report feeling apathetic, emotional indifferent, relieved from painful emotions, a sense of numbing of the emotions, a suppression or absence of emotional life, or a reduction in overall emotional sensitivity.[28,38–46] The fading of these effects – whether they were helpful to the patient or not – and the transition to the unmedicated mind and emotions upon discontinuation of the drug may also introduce potential challenges. In addition to identifying, minimizing, and overcoming withdrawal symptoms, such psychological challenges should also be considered in interventions and guidance aimed at helping patients withdraw from antidepressants safely.

**Interventions used to support antidepressant discontinuation**

Discontinuation of antidepressants has been studied in the context of various psychological interventions as supportive measures, including cognitive behavioral therapy (CBT),[47–50] preventive cognitive therapy (PCT),[51] lifestyle modification,[50] and mindfulness-based cognitive therapy (MBCT) with tapering support.[52–54]

Traditional CBT, as the name indicates, targets psychological disorders at the thought- and the behavioral level, assuming an interplay between thoughts, feelings, physical sensations, and behavior in what has been called the cognitive diamond.[55] These dynamics, when maladaptive and causing distress, can be targeted by challenging and changing both the content of negative thoughts and the underlying core beliefs and the maladaptive coping strategies used by the patient when in distress, which are believed to maintain psychological disorders. Thus, thinking differently about an event and consequently behaving differently are the main goals of therapy, which is usually manualized.[55] One component of CBT is helping patients identify and cognitively restructure erroneous appraisals of threat, including feared bodily sensations.[49,55] This technique, among other adaptive coping strategies in CBT, may be relevant to help patients overcome potential withdrawal symptoms during antidepressant discontinuation. Sequential implementation of CBT following pharmacotherapy has been shown to reduce the risk of depression relapse compared with monotherapy with antidepressants.[56] Furthermore, relapse rates appear to be lower following CBT-assisted discontinuation of antidepressants compared with discontinuation in standard clinical management,[14,47,50] but randomized trials are very scarce and small.[14]

PCT is a version of CBT, also manualized, that focuses on relapse and recurrence prevention by targeting the underlying vulnerability rather than the acute depressive episode.[51] Therapeutic methods include identifying and evaluating dysfunctional attitudes and core beliefs, enhancing retrieval of positive memories and activation of schemas of positive affect, and

specific formulation of a personal prevention plan – however, not involving mindfulness meditation as in MBCT or a primary focus on challenging negative thought content as in CBT.[57]

MBCT is a manualized, group-based, psychological intervention for depression specifically developed to reduce the risk of relapse and recurrence through skills training in mindfulness meditation.[58] Unlike CBT, MBCT does not involve challenging the content of negative thoughts or beliefs or conducting exposure experiments, but teaches acceptance, awareness of negative thought patterns, emotions, and bodily sensations; non-judgement, and attentional control as ways of disengaging from the negative modes of mind and unpleasant emotional states that can trigger relapse or recurrence after remission of the acute depressive episode. The treatment rationale is to teach patients the skills that prevent depressive relapse or recurrence, thus potentially providing an alternative to maintenance antidepressant medication, which some RCTs have found.[52,53] MBCT has been shown to reduce the risk of depressive relapse and recurrence at 12 months compared with placebo or usual care, particularly in patients having experienced three or more depressive episodes.[59]

Lifestyle modification as an intervention focuses on the potential negative effects of a maladaptive lifestyle on mental health, including life stress, excessive work, inadequate rest, and interpersonal friction.[50,60] Relapse or recurrence after remission of the acute depression may occur if such behaviors persist despite antidepressants having restored normal mood, making the patient's lifestyle the primary target of psychological intervention when the antidepressant is discontinued.[50,60]

Other supportive interventions for antidepressant discontinuation include benzodiazepines to counteract potential insomnia,[3,61] switching from pills to liquid formulation to allow smaller and more precise dose reductions,[62] a guided medication review in primary care to identify potential inappropriate drug treatment,[63] a recommendation letter and tapering advice sent to primary care clinicians,[64] and tapering strips.[65,66] A tapering strip is a prepacked strip of 28 day doses that each day are either slightly smaller (down to 0.1 mg) or the same as the previous day, allowing tapering with very small dose reductions compared to the standard manufactured pills.

**Antidepressant use**

Prescription rates have doubled in western countries between 2003 and 2013[67] and continue to rise.[68] In 2016, every tenth Danish adult over 25 years were prescribed an antidepressant,[69] and between 2019 and 2020, prescriptions for antidepressants for any indication increased slightly from 420000 to 426000 people in Denmark.[70] Recent prescription rates among adults in other countries were 16% in the UK,[13,71] 12.7% in the US,[72] 12.7% in Belgium,[13,73,74] and 16.8% in Australia.[75] A particularly high consumption of antidepressants is seen in nursing homes, where

approximately 40% of the residents in Belgium,[76] Sweden, Norway, France,[77] and the US[78] were prescribed an antidepressant. Some studies report even higher consumption rates.[77]

An overall increase in treatment duration has been suggested as a primary driver of the increased antidepressant drug use,[75,79,80] which has raised concerns.[79,81] Thus, half of patients on antidepressant in the US continue taking the drug for more than five years;[82] nearly half in UK continue for more than two years;[63] and in Australia, the average treatment duration is approximately four years.[79]

**Primary indications of antidepressant treatment: Depression and anxiety disorders**

Antidepressant drugs are primarily used in the treatment of depression and anxiety disorders.

Depression is a common, debilitating, and costly mental health problem, primarily due to its relapsing and recurring nature. It is characterized by emotional, cognitive, and neurovegetative symptoms. According to the current Diagnostic and Statistical Manual of Mental Disorders (DSM-5),[83] diagnosis of major depressive disorder (MDD) requires depressed mood or loss of pleasure or interest in almost all activities and at least five of the following symptoms nearly every day, most of the day for two weeks:

- Changes in sleep (e.g., insomnia or hypersomnia)
- Changes in appetite or weight (e.g., decreased or increased)
- Difficulty concentrating or thinking or indecision
- Fatigue or decreased energy
- Changes in psychomotor activity (e.g., slowing or agitation)
- Feelings of worthlessness or inappropriate guilt
- Having recurrent thoughts of death or suicide ideation or actual suicide plans or attempts.

Symptoms must cause clinically significant distress or impaired functioning and not be due to substances or other medical conditions. The severity of a major depressive episode is generally graded as mild, moderate, or severe, based on the number and severity of symptoms and the degree of functional impairment of usual working and social activity.[83]

Global prevalence is estimated to be more than 300 million people,[84] with a lifetime prevalence and 12-month prevalence of 20.6% and 10.4%, respectively, among adults in the US.[85] Some studies, conducted between years 1992 and 2010, suggest that up to every fifth teenager experiences depression sometime during adolescence.[86–88] In 2011, WHO estimated that depression will rank the first cause of worldwide disease burden in 2030,[89] making depression one of the leading contributors to functional disability and causes of burden of disease.[90] The costs due to depression in the US alone is estimated to exceed 210 billion US dollars,[91] and the UK National Health Service has estimated spending £267 on antidepressant prescriptions in 2016.[92]

The indication of antidepressant treatment of depression varies between countries and guidelines. In Denmark, antidepressants are used as first-line treatment for moderate to severe depressive episodes, and used for mild depressive episodes only when psychotherapy has been proven ineffective in the patient or if symptoms are chronic.[93–95] The World Health Organization (WHO) recommends considering antidepressants only after having tried psychoeducation, reducing stress, strengthening social supports, promoting functioning in daily activities and community life, and if symptoms persist or worsen despite psychosocial intervention.[96] According to the NICE guideline on depression in adults, the main indications of antidepressant treatment are patients with a) history of moderate or severe depression, b) persistent subthreshold depressive symptoms lasting longer than 2 years, or c) mild depression or subthreshold depressive symptoms that persist after other interventions.[97] Other indications are severe and complex depression, risk to life, and severe self-neglect.[97] Meanwhile, the American Psychiatric Association (APA) recommends antidepressants as first-line treatment for both mild, moderate, and severe depression, and in the presence of significant sleep or appetite disturbances, agitation, anticipation of maintenance therapy, patient preference, co-occurring disorders, psychosocial stressors, and a history of prior positive response to antidepressants.[98]

Approximately half of patients experience multiple depressive episodes,[99,100] making relapse prevention an inherent part of treatment. Thus, antidepressant treatment of depression generally consists of three phases: The acute phase, the continuation phase, and the maintenance phase.[98] When symptoms have resolved and remission is achieved in the acute phase, typically within 6 to 12 weeks when the treatment is effective, the following 4 to 9 months of continuation treatment is aimed at preventing relapse, while the final maintenance phase is aimed at preventing recurrence of a new depressive episode.[98] Maintenance antidepressant treatment is generally recommended for patients who have experienced more than three depressive episodes or show additional risk factors, e.g., residual symptoms, co-occurring disorders, ongoing psychosocial stressors, onset at an early age, suicide risk, and family history of depression.[98] The recommended duration of each treatment phase varies between guidelines. NICE recommends at least 6 months of continuation treatment and at least 2 years of maintenance treatment if the risk of relapse is high,[97] whereas WHO recommends at least 9-12 months of antidepressant treatment.[96] In Denmark, *Lægehåndbogen* (the doctor's handbook) recommends 6-12 months of continuation treatment and possibly several years of maintenance treatment in case of recurrent depression or psychotic depression.[93] Finally, the Danish Health Authority recommends up to 2 years of antidepressant treatment.[94]

The second most frequent indication of prescribing antidepressants is anxiety disorders[101,102] like generalized anxiety disorder (GAD), panic disorder, agoraphobia, obsessive-compulsive disorder (OCD), and social anxiety disorder – generally as second-line treatment modality after

CBT, but in some guidelines also as first-line treatment (see below). Anxiety disorders are characterized by anxious and fearful emotions and various behavioral disturbances as responses to the distress, which present in different situations and for a variety of objects, depending on the specific disorder. Together with depression, anxiety is considered a 'common mental disorder' by the WHO, with an estimated global prevalence in 2015 of 3.6% and a total of 264 million people living with an anxiety disorder, which was an increase of 14.9% compared with 2005.[84] Anxiety disorders ranked as the 6th largest contributor to global disability and lost health in 2015.[84] Further increases in both prevalence and overall burden have been found during 2020 due to the COVID-19 pandemic, with an increase of 25.6%, or 76.2 million additional cases (to 374 million total), compared with pre-COVID, where the estimated global prevalence was about 298 million people.[103] Furthermore, a recent metaanalysis of epidemiological studies found a point prevalence of 3.3% for severe anxiety disorders, 2.2% for moderate anxiety disorders, and 6.8% for mild anxiety disorders (all without comorbid depression).[104]

One major anxiety disorder is GAD, defined in the DSM-5 as excessive and difficult to control worry and anxiety about different and unspecific events and activities, in addition to at least three of six symptoms:

- Restlessness, feeling keyed up or on edge
- Being easily fatigued
- Difficulty concentrating or mind going blank
- Irritability
- Muscle tension
- Sleep disturbance.[83]

Other diagnostic criteria are that symptoms must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning, must not be explained by other medical conditions or substances, and that the worrying and anxiety must occur on more days than not for at least 6 months.[83]

Indications of antidepressant treatment of GAD in the NICE guideline[105] are as second-line treatment in patients whose symptoms do not respond to psychoeducation, active monitoring, or low-intensity psychological interventions (individual non-facilitated self-help, individual guided self-help, or psychoeducational groups), and as first-line treatment when the disorder causes marked functional impairment. Other indications for drug treatment, possibly in combination with psychotherapy, are complex and treatment-refractory GAD with high risk of self-harm or suicide, self-neglect, significant comorbidity, or other very marked functional impairments. A continuation phase of at least one year after remission is recommended to prevent relapse.[105] In Denmark, antidepressants are recommended as second-line treatment for

GAD after having tried CBT in guidelines concerning both children and adolescents[106] and adults.[107,108]

Another major anxiety disorder is panic disorder, defined in the DSM-5 as having had at least two recurring and unforeseen panic attacks and either a) subsequent worrying, for at least one month, about additional panic attacks or their consequences or b) a significant and maladaptive behavioral change in relation to the panic attacks (e.g., avoidance). Furthermore, the panic attacks must not be explained by substance use, another medical condition, or other psychological issues.[83]

In their guideline for treatment of patients with panic disorder, APA recommends both SSRIs, SNRIs, TCAs (see definitions below), or benzodiazepines over at least a year following acute response, stating that the clinical effects are comparable across the four drug classes and that the evidence is inconclusive to recommend any intervention over another.[109] In the Danish Health Authority's guideline on anxiety in adults, the indication of SSRIs is as second-line monotherapy after ineffective CBT.[107]

Other indications of antidepressant treatment of anxiety disorders include SSRIs as first-line treatment for OCD in the APA guideline;[110] SSRIs as second-line treatment after low intensity treatment (e.g. brief individual CBT) for adults with OCD or as first-line treatment in patients with moderate functional impairment in the NICE guideline;[111] SSRIs as second-line monotherapy after CBT in adults with social anxiety disorder and agoraphobia in the Danish health authority's clinical practice guideline on anxiety in adults;[107] SSRIs or SNRIs in combination with CBT as second-line treatment after CBT for various anxiety disorders in the Danish Health Authority's guideline on treatment of anxiety in children and adolescents;[112] and SSRIs as second-line treatment after CBT for adult patients with social anxiety disorder or patients who prefer pharmacotherapy over CBT in the NICE guideline.[113]

**Different types of antidepressant drugs and their presumed mechanisms of action**

Antidepressant drugs are grouped in different classes with varying pharmacodynamics, although the exact antidepressant mechanism of action remains unknown.[114]

Most antidepressants target the monoamine neurotransmitters (primarily serotonin and norepinephrine, but also dopamine) which early were believed to be involved in mood disorders due to the monoaminergic-enhancing effects of two specific drugs that appeared to have antidepressants properties: The tricyclic antidepressant (TCA) imipramine[115] and the monoamine oxidase inhibitor (MAOI) iproniazid.[116] TCAs increase synaptic monoamine levels, mainly serotonin and norepinephrine, by inhibiting the reuptake of these neurotransmitters back into the presynaptic neuron through the serotonin transporter (SERT) and the norepinephrine transporter (NET), and MAOIs increase synaptic monoamine levels by inhibiting the activity of

the monoamine oxidase enzymes which function to catabolize the monoamines. Thus, when two pharmacologically different drugs appeared to both have antidepressant effects and increase synaptic monoamine levels in the brain, a relationship between monoamines and depression was theorized.[116] Other TCAs include nortriptyline, amitriptyline, desipramine, and clomipramine, and other MAOIs include moclobemide, phenelzine, and tranylcypromine.

Later antidepressants were innovated to increase serotonin selectively via very high affinity for SERT inhibition, resulting in the first selective serotonin reuptake inhibitor (SSRI), fluoxetine, being approved by the FDA in 1987. Thus, the SSRIs extended the pharmacodynamic principle of the TCAs, but with increased receptor selectivity: as neurotransmission is primarily terminated via neuronal reuptake, blocking of this mechanism (by binding to the transporter) leads to enhanced and prolonged serotonergic neurotransmission and postsynaptic stimulation.[29] Other SSRIs are sertraline, paroxetine, citalopram, escitalopram, and fluvoxamine. SSRIs are currently the first-line drug treatment for depression and anxiety disorders due to overall comparable effects and increase tolerability and safety over TCAs and MAOIs.

In 1994 and 2004 followed the dual acting serotonin-noradrenaline reuptake inhibitors (SNRIs) venlafaxine and duloxetine, which have a broader receptor binding profile than the SSRIs, including higher affinity for inhibition of NET and the dopamine transporter (DAT) in addition to SERT.[117] Other SNRIs with indications for depression are milnacipran, desvenlafaxine (the active metabolite of venlafaxine), and levomilnacipran, and the affinity for the different receptors varies between the drugs. While venlafaxine, desvenlafaxine, and duloxetine are several folds more selective for SERT over NET, milnacipran is almost equipotent in its affinity for NET and SERT and do not target dopamine directly.[117,118] For all SNRIs, the weakest affinity is for DAT.

Recently, the serotonin modulators vilazodone and vortioxetine were approved as antidepressants in the US in 2011 and 2013, respectively. In addition to inhibiting SERT, these compounds also modulate the specific subtypes of serotonin receptors believed to be particularly involved in the antidepressant response, e.g., 5-HT1A, 5-HT2A, 5-HT1B, 5-HT17, and 5-HT2C, either as agonists or antagonists.[119] This concept was already known from the serotonin antagonist and reuptake inhibitors (SARIs) like trazodone, approved in the US in 1981, which also both agonizes and antagonizes different serotonin receptors and inhibits SERT, while also antagonizing adrenergic receptors and the histamine H1 receptor.[120]

Other classes of antidepressants, often termed atypical antidepressants, include the norepinephrine reuptake inhibitor (NRI) reboxetine; the norepinephrine-dopamine reuptake inhibitor (NDRI) bupropion, which also antagonizes nicotinic acetylcholine receptors;[121] the melatonergic agent agomelatine, which also antagonizes the 5-HT2C receptor and appears to promote the release of dopamine and noradrenaline in the frontal cortex specifically;[122,123] the

noradrenergic and specific serotonergic antidepressant (NaSSA) mirtazapine, which, among numerous other pharmacodynamics, has also been shown to increase dopamine release specifically in the prefrontal cortex and has high affinity for the histamine H1 receptor, resulting in sedative and hypnotic properties;[114,124] and the recent NMDA-glutaminergic antagonists esketamine and ketamine, which are approved by the FDA for treatment-resistant depression and MDD with suicidal ideation or behavior in adults.[125]

Thus, different classes of antidepressants and different drugs within the classes vary in their affinities for different receptors, yet no drug is completely selective. Rather, selectivity is defined as the ability of a drug to affect a particular cell population in preference to others,[126] e.g., SSRIs as drugs with affinity for SERT at least two orders of magnitude higher than for other receptors.[127] Furthermore, the receptor binding profiles of virtually all antidepressants, including SSRIs and SNRIs, extend beyond the monoamine systems.[128,129] Many antidepressants have affinity also for various post-synaptic serotonin or dopamine receptors,[128] muscarinic acetylcholine receptors and cholinergic receptors,[130] histamine receptors, and sigma receptors.[131,132] Other biological effects of prolonged SSRI treatment, for example, that have been found or theorized include increased neurogenesis[133,134] and increased expression of BDNF and other neurotrophic factors.[135,136] Finally, the time lag of weeks or months between administration of the drug and clinical effect led researchers to look for the mechanism of action in some downstream or adaptational response to the acute drug effect, e.g., downregulation or desensitization of postsynaptic receptors or other neurophysiological changes that occur after prolonged presence of the drug, rather than the acute drug effect itself.[31,137]

**Biological, social, and psychological underpinnings of depression**

A biopsychosocial approach to depression acknowledging the interplay between biological, social, and psychological processes is generally accepted in an overall diathesis-stress hypothesis. That is, certain biological and/or psychological factors may constitute a diathesis, or disposition, towards depression in a person, which may or may not get triggered by different psychological or social factors, e.g., stressors, traumas, and negative life events. For example, longitudinal studies suggest that bereavement leads to depression in about 20 to 25% of people,[138–140] and it may be that this subgroup of people share some biological or psychological predisposition(s) that moderate the relationship between stressors and the depression occurring. Furthermore, whereas the first and often second depressive episodes are usually triggered by some negative life event, the third and following episodes often occur without apparent stressors or triggers in terms of actual events that occur.[58,141]

Various biological and biochemical processes have been theorized to underpin depression, including neurotransmitters, inflammation, the immune system, the endocrine

system, the gut-brain axis and the microbiome, neurocircuitry, hypothalamic-pituitary-adrenal (HPA) axis dysfunctions, the circadian rhythm, neurotrophic factors, and genes.[142–145] The different theories do not exclude each other, as no one unified hypothesis of depression is suggested, but actually argued against.[142] The neurotransmitters involved in mood regulation, mainly serotonin, norepinephrine, and dopamine, constitute one major suggested biological underpinning and pathophysiology of depression.[146] These neurotransmitters are regulated by the corresponding monoamine transporters SERT, NET, and DAT as described above. Thus, from a biological perspective, dysregulation in mood and emotions may involve dysregulation in the relevant monoamines, which may further involve dysregulation in the mechanisms responsible for regulating the monoamines. Consequently, depression is understood, to some extent, as impaired monoaminergic neurotransmission, although the original monoamine hypothesis is now generally considered too simplistic.

Other possible biological underpinnings of depression include impaired and diminished functioning of the hippocampus, potentially caused by stimulation of proinflammatory cytokines which have been suggested to diminish neurogenesis and reduce dendritic sprouting.[147,148] Furthermore, sensitization of the HPA axis[149] and epigenetic DNA methylation (causing reduced genetic expression) of glucocorticoid receptor genes[150] have both been linked to the relationship between early childhood trauma and depression. Such biological changes may predispose people to overall stronger emotional responses and an impaired ability to cope with and regulate future stressors.[151]

Psychological models of depression have, since the advent of CBT in the 1960s, generally focused on maintaining factors of depression, e.g., excessive negative automatic thoughts, dysfunctional schemas and core beliefs that filter how the patient interprets the world, the future and him- or herself,[55] psychological inflexibility,[152] maladaptive or insufficient emotion regulation skills,[153,154] and dysfunctional emotional schemas[155] or metacognitive beliefs.[156] Depression is generally understood as an emotion regulation disorder where mood and emotions, for some reason, do not normalize and regulate naturally (hence the duration criteria in the diagnostic manuals)[83,157] after some major negative life event or series of negative life events (see social underpinnings of depression below). A maladaptive emotion regulation style or negative schema of the world, self, and future can keep the depression symptoms going, that is, maintain the disorder, which is what psychotherapy generally aims at disrupting by introducing various adaptive emotion regulation strategies and restructuring underlying schemas and core beliefs. Cognitive theory, which have dominated the field for decades, focus on the presence and content of dysfunctional, negative thoughts and beliefs as the primary psychological underpinnings of depression. Conversely, several recent psychological models and interventions focus instead on beliefs concerning the nature of cognition (metacognitive beliefs)[156,158] and emotion (emotional schemas)[155,159] itself rather than their content as the main

drivers of impaired emotion regulation and thus depression. Other suggested psychological underpinnings of depression include lack of agency,[160] external locus of control,[161,162] learned helplessness.[163]

Social underpinnings of depression may involve traumatic experiences, major losses, crises, or other negative life events; harassment, poor attachment, adverse childhood experiences, abuse, discrimination, employment status, marital status, insufficient social support, or dysfunctional interpersonal relationships,[164] all of which may potentially function as triggers of depression under certain combinations with other biological or psychological dispositions. In the biopsychosocial model, no 1:1 relationship between any factor – biological, social, or psychological – and development of depression is assumed. Rather, social stressors interact with the individual's vulnerability, potentially triggering depressive symptoms if the stressors exceed the vulnerability threshold.[165,166] As well as acting as triggers, the various adverse social events and situations, too, may make the individual vulnerable to developing depressive episodes if additional stressors occur. Generally, the biological, social, and psychological domains interact with each other. For example, excessive psychosocial stress can activate inflammatory cytokines, stimulate BDNF and other growth factors, and stimulate the release of hormones related to the HPA axis, which have all been associated with depression.[144,167] Likewise, uncontrollable and chronic stress or major traumatic events may lead to the formation of negative and maladaptive schemas and beliefs, the emotional consequences of which may further trigger various neuroendocrine and inflammatory processes.[167,168]

## Objectives

Acknowledging the difficulties many patients face when withdrawing from antidepressant drugs, the aim of this PhD was to investigate three research questions of potential relevance for optimizing the success rate of antidepressant drug withdrawal. The objectives were to address the following research questions:

Project 1: What is the relationship between dose and serotonin transporter occupancy of antidepressant drugs?

Project 2: Does major clinical practice guidelines on depression provide guidance on how to taper and discontinue antidepressant drugs? What is the extent, nature, evidence-base, and quality of such recommendations?

Project 3: Can psychiatric drugs be conceptualized as emotion regulation strategies with respect to their psychoactive and psychological effects in a drug-centred model? How do psychiatric drugs theoretically impact on emotion regulation and how does that relate to psychopathology and psychotherapy?

## Description and methods of the research project

Projects 1 and 2 are systematic reviews, involving quality assessments of the included studies. The reporting of the systematic reviews followed the PRISMA guidelines. Project 3 is a narrative review where we applied emotion regulation research in a discussion of how psychiatric drugs work, based on a drug-centred model.

**Article 1.**

**The relationship between dose and serotonin transporter occupancy of antidepressants – a systematic review**

Protocol: https://osf.io/2f7k5/?view_only=cb987f4a428c4d369b34926b132382c8

In this systematic review we investigated the relationship between dose and serotonin transporter (SERT) occupancy of antidepressant drugs as measured in PET and SPECT studies. The article was accepted for publication in Molecular Psychiatry in August 2021.

We included PET and SPECT studies using highly selective radiotracers ([$^{11}$C]-DASB, [$^{123}$I]-ADAM, or [$^{11}$C]-MADAM) in an *in vivo*, within-subjects design to measure SERT occupancy of any antidepressant at any dose in humans administered orally. We searched PubMed and Embase up to 20 May 2021 and scanned the reference lists of included study

reports and relevant review articles. The search terms are presented in the article and the protocol.

Two researchers independently screened the titles and abstracts for eligibility and extracted the following data from articles meeting our inclusion criteria: Drug name, dose, SERT occupancy (%), brain region, plasma- or serum concentration, $ED_{50}$ values, duration of drug intake, time lag between last dose administration and scanning, type of scan (PET or SPECT), ligand ([$^{11}$C]-DASB, [$^{123}$I]-ADAM, or [$^{11}$C]-MADAM), reference model used to quantify SERT binding potential, study characteristics (availability of a study protocol, assessment of drug adherence, time of day of scan, fasting regimen used), participants characteristics (age, sex, diagnosis, smoking status, alcohol use, and other medications used), authors, and year of publication. In case of missing data, we contacted the corresponding author. In case occupancy was only illustrated in graphs, but not presented in numbered percentages and the corresponding author did not reply when we requested the data, we used a web plot digitizer to derive the occupancy measures from the graphs (this was done in one study).

For studies measuring occupancy of the same drug and dose, we summarized the mean (SD) occupancy at different doses and brain regions for each drug. We presented the data in tables and visualized the dose/occupancy relationship in figures, fitted by a 2-parameter Michaelis-Menten equation as visual overlay to the unique data plots. The Michaelis-Menten model was implemented via the dose-response models (drm) R package using the formula:

$$f(x, K, V_m) = \frac{V_m x}{K + x}$$

where $V_m$ is the horizontal asymptote (expressing maximum occupancy), x is the dose, and the parameter K is the dose corresponding to an occupancy halfway between 0 and $V_m$.[169]

In addition, we compared the decline rates of occupancy vs. plasma/serum concentration using data from the studies that measured occupancy at different time points after dose administration. We visualized the decline rates in graphs by plotting the occupancy and plasma/serum concentration values against time using MS Excel™.

We informally ‘quality assessed’ the studies based on whether they reported transparently on a number of factors that may affect the dose/occupancy relationship (e.g., smoking, alcohol, other medications, duration of drug intake, fasting regimen, duration between drug administration and scanning, age).

**Article 2.**

**Clinical practice guideline recommendations on tapering and discontinuing antidepressants for depression: a systematic review**

Protocol: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=220682

In this systematic review we investigated whether, and to what extent, major clinical practice guidelines (CPGs) on depression cover the issues of tapering and discontinuing antidepressants.

We conducted a multi-tiered literature search on websites of the national health authority, the national psychiatric association, and the national psychological association in seven predefined, English-speaking, high-income countries (the UK, the US, Canada, Australia, Singapore, Ireland, and New Zealand); the websites of major international professional organizations and societies; 14 guideline registries (National Institute for Health and Care Excellence, Standards and Guidelines Evidence, American College of Physicians Clinical Practice Guidelines, National Health and Medical Research Council, New Zealand Guidelines Group, eGuidelines, Guidelines.co.uk, Guidelines International Network Library, Scottish Intercollegate Guidelines Network, the former National Guideline Clearinghouse (now hosted at www.ahrq.gov), Canadian Medical Association Infobase, National Library for Health Guidelines Finder, Best Practice Guidelines, and Magic); and PubMed.

The search terms for PubMed were: (Depression[TI] OR "Depressive Disorder"[Mesh] OR "Depression"[Mesh]) AND (guideline[Publication Type] OR guideline*[TI]). Guideline registries were searched for 'Depression' when a search function was available and manually through all available guidelines when there was no search function. Websites were searched manually. We also searched the first 100 hits on Google on 'depression' and 'guideline'. All sources were last searched on 25 May 2021. For list of all searched sources and websites, see Supplementary Table 1. For excluded CPGs with reason, see Supplementary Table 2.

We scanned the references of included CPGs and relevant systematic reviews. In addition to the CPG documents, we retrieved all associated companion articles to obtain full information on methodology, background, and the guideline development process and group.

We used the PICAR framework for systematic reviews of guidelines to determine our in- and exclusion criteria (Table 1).[170]

**Table 1.** PICAR inclusion criteria

| | |
|---|---|
| **Population and clinical indication** | Patients with depression<br>Any age<br>Any symptom severity |
| **Interventions** | Antidepressant treatment |
| **Comparators, comparisons, and content** | *Comparators:* Any, including none<br>*Key content:* Guidance on tapering or discontinuing antidepressants |
| **Attributes of eligible CPGs** | *Language:* Available in English<br>*Year of publication:* Most recent from each organization<br>*Publishing region:* English-speaking, high-income countries<br>*Version:* Latest version only<br>*System of rating evidence:* Any<br>*Scope:* Must have primary focus on treatment of depression<br>*Recommendations:* No restrictions; CPGs will be included regardless of whether they contain guidance on tapering and discontinuation or not |
| **Recommendation characteristics** | *Duration of treatment:* No restrictions<br>*Levels of confidence:* No restrictions<br>*Interventions:* No restrictions<br>*Comparators:* No restrictions; recommendations are not required to compare an intervention of interest to another intervention<br>*Locating recommendations:* Within CPG text, tables, algorithms, or decision paths |

Screening of titles and abstracts, determining eligibility, data extraction, categorization of the recommendations, and quality assessment were done in duplicate by two researchers independently. We followed a pre-piloted data extraction form with the following data: Guideline title, year of publication, source/organization, country of origin, authors, funding source, conflicts of interest, guidance on: when to consider stopping antidepressant treatment; duration of maintenance treatment after remission; duration of taper; suggested dose reductions; tapering regimen (gradual, linear, hyperbolic); actions if withdrawal symptoms emerge; actions if deterioration or relapse occurs, and mention of: risk of confounding withdrawal symptoms with relapse due to symptomatic overlap; benefits and harms associated with tapering or discontinuation; psychological challenges to stopping antidepressant treatment; and peer-support as a potential supportive measure.

We copied all quotes related to recommendations and information on antidepressant tapering and discontinuation into a table (see Supplementary Table 3) and organized them under categories in MS Excel™ according to our data extraction items. We

summarized the recommendations on tapering and discontinuing antidepressants in a recommendation matrix and the prevalence of each type of guidance in the included CPGs in tables, illustrated in a pie chart.

Using the AGREE II tool,[171] we appraised the quality of the included guidelines that provided guidance on tapering or discontinuation. We followed the AGREE II User's manual[45] and calculated a final score for each of the six domains in each CPG by summing the scores of the two researchers for each of the 23 items and scaling it as a percentage of the maximum possible score (percentage = obtained score – minimum score/maximum possible score – minimum possible score x 100). We pre-defined 'High quality' as >70% on all domains, which is one among three suggestions in the AGREE II user's manual.[172] We also calculated the mean (SD) scores for each domain across the included CPGs. We used the quality scores to identify and discuss major issues and limitations in the CPGs.

**Article 3.**

**The psychology of psychiatric drug action – a narrative review of psychiatric drugs as emotion regulation strategies**

In this narrative review we theoretically explored an alternative model of psychiatric drug action, the drug-centred model, in a psychological and an emotion regulation context. Our basis for conducting this project was the apparent empirical challenges facing the medical model of psychiatric drug action and the fact that implicit assumptions of how psychiatric drugs work are rarely discussed explicitly. Potential mechanisms of action related to the psychoactive effects and the psychological effects of psychiatric drugs have received almost no attention in academia, while emotion regulation research has increased rapidly in recent decades. Given that all psychiatric drugs have psychoactive properties, emotion regulation research may be applicable in the discussion of how psychiatric drugs, including whether – or when – the different drugs constitute adaptive or maladaptive emotion regulation strategies, respectively.

We presented both the medical (or 'disease-centred') model and the drug-centred model of psychiatric drug action and reviewed key empirical support and empirical anomalies of both. We outlined the psychoactive and potential psychological effects of various psychiatric drugs and discussed their potential conceptualization as emotion regulation strategies rather than as disease-targeting treatments. We explored theoretically how drugs may impact on emotion regulation according to two contemporary evidence-based psychological models of psychopathology (the metacognitive model and the emotional schema model) and discussed the potential implications of the drug-centred model on treatment rational and withdrawal. Thus, rather than generate new knowledge, we applied existing knowledge on emotion regulation in

the discussion of what psychiatric drugs do with respect to their psychoactive and psychological effects.

Acknowledging the small and suggested clinically insignificant drug-placebo difference of antidepressants, we further aimed to explore theoretically how antidepressants may exert some of their therapeutic effects via non-pharmacological or psychological mechanisms unrelated to the chemical substance itself, but inherently tied to the pill and the diagnostic context around it.

## Summary of results and discussion

**Article 1.**

**The relationship between dose and serotonin transporter occupancy of antidepressants – a systematic review**

**Major findings**

We included 17 PET and SPECT studies and found a hyperbolic relationship between dose and SERT occupancy for all the 10 different antidepressants we reviewed (including SSRIs, SNRIs, and serotonin modulators). Mean occupancy at the lowest standard manufactured dose ranged between 51±10% and 93±8%, depending on the drug (Table 2, using repeated dosing data), after which it plateaued at approximately 80-85% for most drugs despite further substantial increase in dose, modelled by the Michaelis-Menten equation (shown in the publication, Figure 1). At half the lowest standard manufactured dose – after the break line – mean occupancy ranged between 49±12% and 73±1% (Table 2). Even at fractions of the lowest standard manufactured doses of down to one tenth of citalopram, one fifteenth of venlafaxine, one fifth of sertraline, one twentieth of fluoxetine, and one sixth of duloxetine, substantial SERT occupancies were measured (Table 3). $ED_{50}$ values occurred at doses below half of the lowest standard manufactured dose of all the antidepressants except vortioxetine (Table 4).

**Table 2.** Serotonin transporter occupancy at lowest manufactured doses

| Drug | Lowest dose (mg) | Occupancy (mean±SD) | | Break line | Occupancy (mean±SD) |
|---|---|---|---|---|---|
| Citalopram | 10 | 61% – 76±9% | | 5 | 67±18% |
| Escitalopram | 5 | 60±6% – 67±7% | | 2·5 | *Not investigated* |
| Sertraline | 50 | 74±6% – 85±7% | | 25 | 72±4% |
| Paroxetine | 20 | 45±21% – 93±8% | | 10 | 60% |

| | | | | | |
|---|---|---|---|---|---|
| Fluoxetine | 20 | 85±9% | | 10 | 73±1% |
| Fluvoxamine | 50 | 76±3% | | 25 | *Not investigated* |
| Venlafaxine | 37·5 | 76±10% | | 18·75* | 66±3% |
| Duloxetine | 30 | *Not investigated, but above the 85±4% of 20 mg* | | 15* | *Not investigated, but above the 44±9% of 5 mg* |
| Vortioxetine | 5 | 51±10% | | 2·5 | 49±12% |
| Desvenlafaxine | 50 | 90±9% | | 25 | 71±13% |

**Table 2 legend:** Where a dose was investigated in one study only, the mean (SD) occupancy of that individual study is presented; where a dose was investigated in multiple studies, the range of means (SDs) from those studies is presented. Ranges represent occupancy from different durations of drug-intake and different radiotracers, with the lower end of the range representing single dose studies and the higher end of the range representing longer durations. Table shows data for the brain region with highest occupancy from individual studies only; for other brain regions and references to individual studies, see table 2 in the article. The minimum doses available for purchase in Denmark were retrieved at www.promedicin.dk.
SD: standard deviation.
*Venlafaxine and duloxetine are usually capsules, not pills, and have no break line.

**Table 3.** Serotonin transporter occupancy at doses below the lowest manufactured doses

| **Drug** | **Dose (mg)** | **N** | **Occupancy range** | **Occupancy (mean±SD)** |
|---|---|---|---|---|
| Citalopram | 1 | 2 | 11 – 20% | 16±6% |
| | 2·5 | 2 | 41 – 42% | 42±1% |
| Sertraline | 10 | 3 | 34 – 58% | 49±13% |
| Fluoxetine | 1 | 2 | 25 – 34% | 30±6% |
| | 2·5 | 2 | 31 – 50% | 41±13% |
| | 4 | 1 | 67% | NA |
| | 5 | 2 | 61 – 69% | 65±6% |
| Venlafaxine | 2·4 | 2 | 16 – 34% | 25±13% |
| | 5 | 2 | 39 – 41% | 40±1% |
| | 10 | 1 | 63% | NA |
| Duloxetine | 5 | 3 | NA | 44±9% |
| | 20 | 3 | NA | 85±4% |

**Table 3 legend:** NA: Not applicable.
Table shows brain region with highest occupancy; for other brain regions see table 2 in the publication.

**Table 4.** $ED^{50}$ for antidepressants

| **Drug** | **$ED_{50}$ (mg)** |
|---|---|
| Citalopram | 3·4 |

| | |
|---|---|
| Sertraline | 9·1 |
| Paroxetine | 5 |
| Fluoxetine | 2·7 |
| Venlafaxine | 5·8 |
| Duloxetine | 7·9 |
| Vortioxetine | 8·5 |
| Desvenlafaxine | 14·4 |

**Table 4 legend:** $ED^{50}$: Effective Dose 50 (the dose corresponding to 50% of maximum occupancy).

It follows that even minor dose reductions in the lower dose range will have large effects on serotonin levels and thus potentially cause withdrawal symptoms, given a relationship between the two, which has been hypothesized, but not yet tested. Discontinuing the drug at the smallest standard available dose, or even after the break line, will result in a sudden and large drop in SERT occupancy, potentially causing severe withdrawal symptoms. Standard available doses of antidepressants thus cannot be used to taper in a pharmacologically rational way, as the doses are too large to secure a gradual and slow unblocking of SERT. This principle likely also applies to other targeted receptors by antidepressants, consequent to the law of mass action.[173] Thus, a linear dose reduction regimen does not gradually reduce the biological effects of antidepressants. Rather, a linear and gradual decrease in occupancy requires a hyperbolic reduction of dose, which involves reducing the dose in much smaller increments than possible with standard available doses.

We also found that plasma/serum half-life did not reflect the occupancy decline rate at the target receptor, as SERT remained blocked longer than it took for the plasma/serum concentration to fade (Figure 2 in the article). For example, between four and 24 hours, occupancy of 10 mg escitalopram only decreased from 69% to 66%, while plasma concentration was halved (from 13,8 to 6,5 ng/mL). After an additional 24 hours, at 48 hours post-dose, SERT was still occupied by 53%, while plasma concentration was further halved to 3,2 ng/mL. Sertraline showed the same pattern, as occupancy at four-, 24- and 48-hours post-dose decreased from 74% to 69% to 57% and plasma concentration from 19,4 to 8,3 to 3,8 ng/mL. The reported half-life of sertraline is 26 hours, but after 24 hours, occupancy was only reduced by five percent. Duloxetine, with the short half-life of 8-17 hours, at 60 mg occupied SERT by 84% at 6 hours, 72% at 49 hours and 47% at 78 hours. Thus, despite being 50% eliminated in the plasma after 8-17 hours, SERT occupancy was not halved even after 78 hours. For paroxetine, the reported half-life is 30-36 hours, and after 48 hours, occupancy only decreased by 16%.

This discrepancy may have implications for the onset of withdrawal symptoms following dose reduction, as the symptoms are theorized to occur upon unblocking of the target

receptors and not the decrease in blood concentration. Predicting the onset of withdrawal symptoms based on half-life is thus faulty, as delayed onset can be expected.

Finally, information on factors that may have affected metabolization and bioavailability of antidepressants, and thus also the dose/occupancy relationship, was not available in most studies. Non-transparent reporting was evident, especially regarding smoking status, alcohol consumption, and comedication.

**Assessment of methods**

We had planned to meta-analyze occupancy data from studies investigating the same drug, dose, and brain region by calculating the summary mean occupancy (with 95% confidence interval) and presenting it in graphs as the summary estimate of occupancy as a function of the different doses. However, study design heterogeneity and too little data precluded meaningful meta-analysis. We therefore synthesized in tables the raw occupancy data in means and standard deviations for the different drugs, doses, and brain regions. To visualize the dose/occupancy relationship, we then plotted occupancy against dose in graphs and modelled the data with a two-parameter Michaelis-Menten equation as visual overlay. Compared with our planned methods, this method has obvious limitations, as the data were not directly modelled, but visually fitted by the predicted Michaelis-Menten model. Furthermore, a 95% confidence interval could not be determined. The ideal metaanalysis would require individual patient data, which we did not succeed in obtaining, and less study design heterogeneity.

Another limitation of our methods was that we synthesized occupancies derived from both single- and repeated dosing, which are likely not entirely comparable and may contribute to heterogeneity, as steady state was not achieved in many participants. This underestimates the overall occupancy measures, meaning that even higher occupancies can be expected in real life patients who take the drugs continuously. Indeed, occupancy increased with treatment duration (with between 3 and 23%) in the three included studies that measured occupancy at different durations of drug intake.[174–176] The conclusion of a hyperbolic dose/occupancy relationship thus remains and is even strengthened by this limitation of including single dose data.

Furthermore, the studies varied in other factors that may contribute to outcome heterogeneity, e.g., different radiotracers, reference models, brain region of interest, subjects' age and sex, time lag between dose administration and scanning, and health status. Regarding mixing depressed and healthy subjects, there is, to our knowledge, no definitive evidence that SERT availability differs between these two groups, also depending on which region is chosen.[177] We also noticed that the included studies that compared pre-treatment SERT availability between depressed and healthy subjects found no such differences;[176,178–180] however, the studies were likely not powered to detect such differences.

Finally, the web plot digitizer we used in one study[178] to derive the occupancy data may not have provided the exact measures, introducing a risk of a slight imprecision of the data - care was taken to target the tool at the exact data points in the graphs.

**Justification of conclusion**

Our main conclusion of a hyperbolic dose/occupancy relationship (i.e., that occupancy increases rapidly in the lower dose range and plateaus at moderate and higher doses) was based on rather few unique data points from the lowest dose range (six subjects at <10 mg citalopram, no subjects at <5 mg escitalopram, five subjects at <50 mg sertraline, three subjects at <20 mg paroxetine, nine subjects at <20 mg fluoxetine, no subjects at <50 mg fluvoxamine, seven subjects at <37.5 mg venlafaxine, 13 subjects at <30 mg duloxetine, 16 subjects at <5 mg vortioxetine, and four subjects at <50 mg desvenlafaxine). More occupancy measures at low doses are therefore needed to fully justify this conclusion, including determining a better estimate of the variation around the mean. However, for occupancy to reach the high values it did on the lowest standard doses (which were the most studied ones) and thereafter plateau at around 80-85%, the increase in the lower doses up to the standard doses would have to be hyperbolic regardless of the scarcity of actual occupancy data. Thus, our conclusion of a hyperbolic relationship following the Michaelis-Menten equation in terms of determining the general behavior of the dose/occupancy curves appears justified, also considering the law of mass action as discussed in the publication. Further strengthening our conclusion is that much of the occupancy data were derived from single dose or short-term studies, meaning that the drug had not reached steady state in many participants as discussed above. SERT occupancy of antidepressants can thus be expected to be even higher than what we found. In addition, the aim of occupancy research cannot be to establish the one true occupancy at any given dose of any drug, as numerous individual factors affect this relationship in any one patient, e.g., genetics, metabolism, age, co-medication, smoking, and alcohol use. A better estimate of the true variation of occupancy between subjects taking the same dose requires minimizing both this heterogeneity and the study design heterogeneity. The non-transparent reporting on the study participants' use of alcohol, tobacco, and co-medication (which may affect metabolization and bioavailability, and thus occupancy) introduces the possibility of having an overall skewed and nongeneralizable study sample.

Moreover, occupancy measures did exceed the apparent plateau at some doses and RoIs in some subjects, e.g., 91% in amygdala at 20 mg citalopram; 88% in amygdala at 10 mg escitalopram; 90% and 91% in striatum at 40 and 60 mg paroxetine, respectively; >91% in prefrontal cortex, midbrain, and bilateral cuneus at 75 mg venlafaxine; 90% and 93% in raphe nuclei at 20 and 60 mg vortioxetine, respectively; 90% and 96% in amygdala at 50 and 100 mg desvenlafaxine, respectively; and between 90 and 97% in all RoIs measured at 150 mg

desvenlafaxine. Furthermore, the variation around these means indicates that even higher occupancies occurred in some individuals, although these data were extremely scarce and not available at the individual level. This suggests that the observed plateau is not an absolute max, and it may be that the critical clinical threshold, both regarding clinical effect and withdrawal symptoms, lies somewhere above the plateau. Conversely, it may also be located below the plateau, but this question cannot be answered from the data we reviewed.

There were no studies of TCAs or MAOIs; drugs where the evidence is also more limited in terms of establishing whether, or to what extent, there is a dose-effect gradient, compared with SSRIs and SNRIs. Thus, our linking between an occupancy plateau and the limited clinical effect of dose escalation above the minimum effective antidepressant dose may not apply to TCAs and MAOIs – where the clinical evidence is less certain and occupancy data lacking –, but only to SSRIs and SNRIs. Based on our literature search, which included search terms for alle antidepressants, SERT occupancy of TCAs and MAOIs have only been investigated in few, biased between-subjects designs and with nonspecific radioligands, which we did not include. The complete lack of reliable in vivo data on the primary biological effect of these drugs is an interesting finding in itself, and it limits our overall conclusions about the relationship between occupancy and clinical effect of antidepressants, which may potentially be stronger for TCAs and MAOIs than for other antidepressants.

The link between SERT occupancy and withdrawal symptoms remains theoretical and without controlled research yet does follow general theory on withdrawal reactions.[1,20,22,24] Only observational studies of so called tapering strips, which allow hyperbolic tapering, have been conducted.[65,66] As discussed earlier in this thesis, it makes sense to look for the mechanism behind withdrawal reactions in a drug's primary biological effect. For most antidepressants, this is SERT antagonism, which raises synaptic serotonin levels. However, whether withdrawal symptoms can occur also upon unblocking of other receptors also targeted by antidepressants remains unknown, but likely (e.g., the norepinephrine transporter, the dopamine transporter, various presynaptic 5-HT receptors, GABA, and receptors related to cholinergic or histaminergic effects). In that case, the dose/occupancy relationship for those receptors must be established. Whether the relationship between dose and secondary receptor occupancy follows the same hyperbolic curve as SERT is unclear from this review, but somewhat likely, consequent to the law of mass action.[173] However, some drugs start occupying other receptors only at certain doses (that is, not starting at 0 mg) due to different affinities and binding profiles for different receptors,[181–184] meaning that the next dose/occupancy relationship – whether hyperbolic or not – would start at that dose, not at 0 mg. A dose reduction regimen following the SERT occupancy curves may thus not correspond to a gradual unblocking of all targeted receptors, thus potentially causing withdrawal symptoms despite a gradual and slow unblocking of SERT. While this questions the idea of larger dose reductions above the plateau,

the rationale for hyperbolic tapering remains; that is, that dose reductions must get smaller and smaller as the tapering progresses. Finally, no sound argument seems to exist for a linear tapering regimen that follows dose as the unit relevant to withdrawal reactions. A pharmacologically rational tapering would have to follow the degree to which certain doses reach their target receptors.

**Contribution to current knowledge and comparison with other studies**

This was the first systematic review of the evidence on SERT occupancy of antidepressants. We provided a complete overview of the evidence, including an assessment of limitations and suggestions for areas of improvement for future occupancy studies. We identified the most reliable, high-quality studies by excluding studies using non-specific radiotracers and the between-subjects design. References to these studies were presented in Supplementary Table 1.

Our findings are consistent with, and provide potential mechanistic insight into, outcomes of dose-escalation trials, which find no or limited clinical benefit of increasing the dose beyond the minimum effective dose for SSRIs. This has been shown using fixed dose regimens,[185,186] a flexible dose regimen,[187] and in non-responders to standard doses as a second-step strategy.[188,189] Side effects, however, do appear to increase with dose above the occupancy plateau,[185,190] presumably due affinity for other receptors than SERT, which may suggest dose reduction down to the plateau as a useful strategy for patients experiencing severe side effects. However, a direct relationship between either clinical efficacy[28,178,189] or adverse events and SERT occupancy has not been shown. We further noticed that the included studies in depressed patients that investigated the relationship between clinical effect and SERT occupancy found no such correlations.[178–180] However, like with the studies comparing pre-treatment SERT availability between depressed and healthy subjects, these studies were likely not powered to detect such correlations.

As discussed above, our findings are also consistent with, and provide potential mechanistic insight into, the occurrence of withdrawal symptoms even at very small dose reductions in the lower dose range.[19,20] A similar approach to tapering has been applied for benzodiazepines[19] and antipsychotics.[191]

In relation to indicating how slow a pharmacologically rational tapering regimen is, our study has implications for all trials involving antidepressant discontinuation as part of the trial design, e.g., traditional relapse prevention trials.[192] Such trials involve an inherent risk of bias of confounding withdrawal symptoms with the outcome measures if the drug is not tapered in a way that optimally mitigate withdrawal symptoms (which is unknown, but may be informed by the present systematic review).

Finally, the discrepancy between half-life and receptor occupancy decline rate has implications for the use of wash-out periods in clinical trials, which aim to secure that the participants' previous drugs are eliminated from the body prior to administration of the study drug. For this rationale to hold, the length of the wash-out period would have to be determined by the occupancy decline rate rather than by plasma/serum half-life as is custom, which would prolong the wash-out period substantially compared with using half-life.

**Article 2.**

**Clinical practice guideline recommendations on tapering and discontinuing antidepressants for depression – a systematic review**

**Major findings**

Of the 21 clinical practice guidelines (CPGs) we included, 15 (71%) recommended a slow or gradual taper when discontinuing antidepressants and informed that withdrawal symptoms can occur, however, virtually no practical guidance on dose reductions was provided. The recommendations were vague and ambiguous, e.g., to taper 'slowly', 'gradually', 'over an extended period of time', 'over several weeks', or over a suggested period of time (ranging between at least four weeks to six months). Tapering recommendations were usually described in one or two sentences withing the whole guideline and without elaborating what a slow or gradual taper means in practice.

The potential symptomatic overlap between withdrawal reactions and relapse was mentioned in only 4 (19%) of the 21 CPGs, and there was no guidance on how to distinguish between these two fundamentally different clinical situations or how to treat them accordingly.

Guidance on how to manage withdrawal symptoms (provided in 5 (24%) of the 21 CPGs) consisted of single statements to 'resume the drug and taper more slowly', 'provide explanation and reassurance', or 'monitor symptoms', but never to provide psychosocial support to help the patient get through the withdrawal period.

We found no mention of any psychological challenges to coming off antidepressants or guidance on how to overcome them.

No benefits of becoming drug-free were considered in any CPG.

Maintenance antidepressant medication (i.e., continuing the drug after symptomatic remission) was recommended in 17 (81%) of the CPGs, with a suggested minimum duration of between four and 12 months, depending on the clinical condition. Thus, most CPGs alluded to that pharmacotherapy should eventually end by suggesting a duration of the treatment, but only two (10%) included a specific statement that the drug should be stopped after maintenance treatment. Likewise, the discontinuation phase of treatment was consistently not mentioned in the treatment algorithms or flow charts.

Overall, current CPGs are inadequate in guiding clinicians to help patients identify, minimize, and manage withdrawal symptoms and psychological challenges to coming off antidepressants.

Guideline quality was low (overall tapering or discontinuation guidance: 17±8%, scope and purpose: 62±20%, stakeholder involvement: 42±23%, rigor of development: 27±12%, clarity of presentation: 21±10%, applicability: 6±8%, and editorial independence: 30±22%). Primary issues in the different domains according to the AGREE II criteria for guideline development are presented in the article's Supplementary Table 4.

**Assessment of methods**

Our inclusion criteria of CPGs from English-speaking and high-income countries were potentially at odds with our aim of including all high impact CPGs. Our findings and proportions thus cannot be generalized to CPGs from other countries, which require separate investigation. Furthermore, what constitutes a major international professional organization or society is subjective. We used our combined knowledge of such organizations, but other researchers may potentially identify other CPGs that they consider major.

We chose one of three suggested cutoff points for defining a 'high quality guideline' in the AGREE II user's manual,[172] however none of them have been validated. Considering the overall low scores on most domains, none of the other cutoff points would have changed the results.

Subjective judgments are inherent in both the AGREE II quality appraisal tool and the categorization of CPG content, and other researchers may have rated and categorized differently. We therefore provided full transparency by presenting all text excerpts from the CPGs pertaining to recommendations and information on tapering and discontinuation (Supplementary Table 3) and the individual domain ratings of each CPG as appraised by both researchers (Supplementary Table 4).

Our study has several strengths. Literature search, screening, data extraction, and quality assessment were conducted in duplicate by two researchers independently; we followed a pre-registered protocol; we provided full transparency of the CPG content we used, our list of excluded CPGs with reason, and our AGREE II quality assessment forms as supplementary information; we updated our literature search prior to writing the final draft of the manuscript, which resulted in one new iteration of an included CPG; and we used a multi-tiered literature search strategy covering both PubMed, various guideline registries, websites of relevant organizations, Google, and references of included CPGs and relevant systematic reviews.

**Justification of conclusion**

Considering what is known about the incidence, duration, type, and potential severity of withdrawal symptoms, our conclusion appears justified that current guidance is inadequate in identifying, minimizing, and managing withdrawal symptoms and thus needs updating. The lack of evidence-based guidance – and guidance in general – is closely tied to the scarcity of relevant research on antidepressant withdrawal in terms of both optimal tapering regimens and supporting interventions. However, much of the research that has been conducted is generally not reflected in the CPGs' recommendations, including the systematic reviews on discontinuation methods, the RCTs aimed specifically at helping patients come off antidepressants, survey studies into patients' experiences with withdrawal and tapering, research on patient narratives as they are expressed on online forums, which we previously investigated regarding protracted withdrawal symptoms,[21] and indirect evidence and theory on receptor occupancy regarding dose reduction regimens. Many of the included CPGs were published at a time when even less was known about safe tapering than today, let alone about the existence of antidepressant withdrawal issues in general, and one would therefore to a lesser degree expect them to include such guidance than newer CPGs. Finally, our conclusion of overall low-quality ratings was based on criteria defined by a formal and validated tool for appraising guideline quality, which is a strength. However, many of the included CPGs were published before the AGREE II tool was launched in 2010, which then cannot be expected to have followed the AGREE II criteria, making the assessment potentially problematic. Still, our conclusions remain in practice; that current CPGs need updating and are of low quality, which is a genuine clinical problem.

**Contribution to current knowledge and comparison with other studies**

This was the first systematic review of guidance on tapering and discontinuing antidepressants in clinical practice guidelines on depression, and to our knowledge the first study into such guidance in general.

Our findings may contribute by identifying and highlighting a major clinical problem in that guidelines recommend pharmacotherapy without providing guidance on how to safely taper and discontinue treatment. This lack of guidance likely contributes to unnecessary long-term antidepressant treatment in some patients, yet to an unknown degree. Better and more concrete guidance, possibly informed by our findings and our AGREE II appraisal, might be helpful in differentiating between the patients who deteriorate due to withdrawal vs. genuine relapse of the clinical condition in clinical practice.

Our call for better guidance and increased attention on withdrawal-related issues is consistent with some recent developments in academia,[193] including several systematic reviews into different aspects of antidepressant withdrawal; a Cochrane review also concluding that research is needed, including on hyperbolic tapering;[13] several ongoing clinical withdrawal

trials,[16,17] also of antipsychotics;[194] and the increasing attention and changed definition of withdrawal symptoms occurring in UK guidelines.[195,196]

**Article 3.**

**The psychology of psychiatric drug action – a narrative review of psychiatric drugs as emotion regulation strategies**

**Major findings**

Key definitions of emotion regulation appeared to match the descriptions of the psychoactive effects of various psychiatric drugs as understood in a drug-centred model of psychiatric drug action and as reported by patients in qualitative interviews. Emotion regulation is defined as 'the processes by which individuals influence which emotions they have, when they have them, and how they experience and express these emotions'[154] and 'actions taken by a person to modify/change emotions or increase or reduce their intensity'.[153] We thus argued that psychiatric drugs – being psychoactive substances that alter emotions, thinking, and behavior – can be conceptualized as emotion regulation strategies, and, as a consequence, evidence from emotion regulation research should be considered applicable to psychiatric drug treatment.

The drug-centred model changes the treatment rationale from disease-targeting treatments to emotion regulation strategies, i.e., that drugs affect psychopathology by superimposing a drug-induced state upon the symptomatic state, which may then be experienced as emotionally appealing and helpful for patients in psychopathology. Drug-induced mental states of reduced and suppressed emotional intensity, emotional numbing, lethargy, sedation, slowed mental activity, reduced arousal etc. make clinical sense as attractors for people experiencing the uncontrollable, overwhelming, experienced intolerable, and incomprehensible emotions and excessive thoughts that characterize much psychopathology transdiagnostically.

Whether medical emotion regulation is adaptive or maladaptive over the long term depends on the individual, the clinical situation, and on how it affects the patient's metacognitive beliefs and emotional schemes that drive psychopathology at a more fundamental level. Psychiatric drugs may succeed in reducing symptoms and making the patient feel better while inadvertently confirming and reinforcing the beliefs that thoughts and emotions are uncontrollable, will last indefinitely and escalate, are intolerable, and make no sense, which psychotherapy aims at modifying. Importantly, these negative psychological effects can occur while symptoms on rating scales are reduced. We thus showed theoretically how psychopharmacology and psychotherapy operate on different levels of the psychopathological process and in ways that may potentially conflict with each other.

Lastly, we hypothesized several possible psychological effects of taking psychiatric drugs and getting diagnosed that may contribute to improvement, e.g., countering rumination by

providing an explanation for one's suffering, initiating a corresponding set of principles for behavior change, starting to share painful feelings and thus breaking isolation, emotional validation, and inducing hope and positive expectations.

**Assessment of methods**

A PhD study, and research in general, is traditionally understood as generating knowledge. In this project, we aimed to use existing knowledge rather than generate more. Our methods were obviously theoretical and philosophical rather than empirical, which we considered appropriate given the current state of the field where underlying treatment assumptions rarely are discussed explicitly, which it was our aim to do. Our primary method was to apply evidence from emotion regulation research in a discussion of how psychiatric drugs work in a drug-centred model.

This paper was prone to the limitations inherent in any narrative review, including having no systematic literature search, no explicit criteria for study selection, no formal or predefined methods to arrive at the conclusions, no quantitative or empirical investigation or analysis, subjective and likely biased selection and interpretation of supporting evidence, and lack of quality assessment of the cited studies. Consequently, our findings (or ideas) and conclusions do not represent a comprehensive understanding or overview of the field but should be considered theories and hypotheses for future research to investigate empirically. We did, however, attempt to search the literature on the different subjects thoroughly and ended up including many references.

Empirical investigation of our research questions and proposed theories is crucial, potentially involving qualitative interviews of patients on various psychiatric drugs regarding their subjective and emotional experience of the psychoactive effects. It would also be relevant to study how patients find the psychoactive / emotion regulatory effects helpful and how these effects impact om relevant metacognitive beliefs and emotional schemes.

Finally, we based our theoretical exploration of potential non-pharmacological mechanisms of action of antidepressants on the outcomes of meta-analyses of placebo-controlled trials, which find no clinically significant difference between antidepressants and placebos (see table 1 in the article). However, these studies have been criticized for, among other things, underestimating the true effect of antidepressants by using the Hamilton Depression Rating Scale 17 (HDRS-17), which allegedly has poor validity, is not sensitive to depression symptoms change, and is not unidimensional.[197–199] We previously investigated this hypothesis in a re-analysis of the studies included in Cipriani et al. 2018[200] that used either the HDRS or the gold standard outcome measure, the Montgomery-Asberg Depression Rating-Scale (MADRS); we found no clinically meaningful difference between these two rating scales.[201] Several other critiques of the interpretation that antidepressants do not outperform placebos regarding clinical significance have been raised and refuted,[202,203] and we thus considered it justified to claim that non-pharmacological mechanisms of action may be involved.

**Justification of conclusion**

Considering the theoretical and narrative setting of this paper, we believe our conclusion can be justified that psychiatric drugs have both psychoactive and psychological effects in addition to their direct biological effects, and that the drugs thus constitute emotion regulation strategies. According to a drug-centred model, it thus appears justified that emotion regulation research is applicable when discussing how psychiatric drugs work.

The degree to which the different mechanisms of action are involved remains unknown and likely varies between patients, contexts, and different drug classes; our focus on these alternative effects does not preclude biological effects from occurring and potentially being relevant to treatment outcomes as assumed in the medical model.

As discussed in the article, the presence of anomalies in the medical model paradigm of psychiatric drug action is undebatable, yet the degree and quality of evidence for and against the model was not addressed in the present study and should thus continue to be discussed and investigated explicitly. However, the identified anomalies justify our attempt to explore alternative models.

Finally, whether the psychoactive effects of different psychiatric drugs can rightfully be conceptualized as emotion regulation is a question of definition which may vary between theories, models, and researchers.

**Contribution to current knowledge and comparison with other studies**

Cf. the background for writing this paper being the predominant focus on the medical model of psychiatric drug action in academia, very few publications compare to our paper, and most of them are written by the last author.

The drug-centred model of psychiatric drug action as presented in this paper was a natural extension of the last author's previous work,[204,205] yet the coupling with emotion regulation research and the conceptualization of psychiatric drugs as emotion regulation strategies has, to our knowledge, never been done before. Neither has the discussion of potential implications for psychiatric drug withdrawal, which is currently focused on the physiological withdrawal symptoms.

Our paper may contribute to the field by expanding the investigation and discussion of psychiatric drug treatment beyond the direct biological effects in a medical model to also including the psychoactive (emotion regulatory) and psychological effects in a drug-centred model, which fit well with an overall biopsychosocial paradigm.

Our approach was consistent with other studies and articles underlining the shortcomings of the medical model[206–210] yet not taking the next step of revising the underlying assumptions of how psychiatric drugs then work. In general, major critiques of the medical model of psychiatric drug action are mostly expressed in books rather than journal articles. However, antidepressants have previously been conceptualized as symptomatic treatment that 'suppress

symptoms'[211] and as a coping strategy under the broader concept of the Cognitive Attentional Syndrome in metacognitive therapy.[156]

## Conclusions and perspectives for further research

Issues related to antidepressant withdrawal, both physiological withdrawal symptoms and psychological challenges, are poorly investigated in the research and inadequately covered in the major clinical practice guidelines. This may lead to unnecessary long-term antidepressant treatment in some patients due to withdrawal symptoms being misinterpreted as relapse, which future research should investigate.

Major clinical practice guidelines on depression provided only scarce and vague guidance on how to taper and discontinue antidepressants. Whereas most guidelines recommended a 'gradual' or 'slow' taper when discontinuing antidepressants, what this means in practice was virtually never specified; there were no guidance on dose reductions. Whereas most guidelines informed that withdrawal symptoms can occur, there were no recommendations on how to distinguish withdrawal symptoms from relapse or how to help patients get through withdrawal symptoms. Consequently, following current guidance on how to taper and discontinue antidepressants likely involves a high risk of causing withdrawal symptoms which there is no guidance on how to distinguish from relapse or otherwise manage. It was clear that the discontinuation phase of antidepressant treatment was not prioritized in the guidelines, as none of the treatment algorithms or flowcharts included tapering or discontinuation. Guideline quality as assessed with the AGREE II tool was overall low, and we documented several areas for future guidelines to optimize.

Better guidance requires more and better randomized trials. Future clinical trials should control for withdrawal symptoms confounding the outcome measures by tapering the drug in a way that optimally mitigate withdrawal symptoms, yet the optimal tapering rate is currently unknown. Receptor occupancy studies may contribute to solving this problem by identifying the doses that correspond to a gradual and slow unblocking of the target receptors, which is hypothesized – but without direct evidence – to mitigate the risk of withdrawal symptoms. We documented in a systematic review that SERT occupancy follows antidepressant dose in a hyperbolic manner, modelled visually by the Michaelis-Menten equation. The high occupancy at low doses implies that very small dose reductions in the lower dose range are likely required to secure a gradual unblocking of the primary target receptor (SERT); whether hyperbolic tapering mitigates the risk of withdrawal symptoms compared with linear or abrupt discontinuation should be investigated directly. However, whether other targeted receptors are involved in the mechanism of antidepressant withdrawal symptoms, too, remains unknown, which questions the idea of tapering directly according to the SERT occupancy curves. More occupancy studies of antidepressant at low doses are needed for all targeted

receptors. Furthermore, to better understand the relationship between antidepressant dose and receptor occupancy, future studies must control for various factors affecting the dose/occupancy relationship, which the current evidence-base did not. Transparent reporting of such factors is a must.

Finally, our proposed model of understanding psychiatric drugs as emotion regulation strategies, which makes theoretical sense, needs empirical investigation, possibly involving qualitative interviews, studies into the impact of psychiatric drug treatment on patients' metacognitive beliefs, emotional schemes, and established emotion regulation strategies, and further theoretical discussion in light of emotion regulation research and definition. Generally, the psychoactive and psychological effects that psychiatric drugs may have on patients need investigation, including whether these effects introduce issues when withdrawing from the drugs.

## Abbreviations

| | |
|---|---|
| SERT | Serotonin transporter |
| NET | Norepinephrine transporter |
| DAT | Dopamine transporter |
| CPG | Clinical Practice Guideline |
| RCT | Randomized Controlled Trial |
| PET | Positron Emission Tomography |
| SPECT | Single Photon Emission Computed Tomography |
| GRADE approach | Grading of Recommendations Assessment, Development and Evaluation |
| AGREE | Appraisal of Guidelines for Research and Evaluation |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| CBT | Cognitive Behavioral Therapy |
| MBCT | Mindfulness-Based Cognitive Therapy |
| PCT | Preventive Cognitive Therapy |
| WHO | World Health Organization |
| APA | American Psychiatric Association |
| NICE | National Institute for health and Care Excellence |
| MDD | Major Depressive Disorder |
| GAD | Generalized Anxiety Disorder |
| OCD | Obsessive Compulsive Disorder |
| FDA | Food and Drug Administration |
| 5-HT | 5-hydroxytryptamine receptors |
| SSRI | Selective Serotonin Reuptake Inhibitor |
| SNRI | Serotonin-Norepinephrine Reuptake Inhibitor |
| TCA | Tricyclic antidepressant |
| MAOI | Monoamine oxidase inhibitors |
| NaSSa | Noradrenergic and Specific Serotonergic antidepressant |
| NDRI | Norepinephrine-Dopamine Reuptake Inhibitor |
| NRI | Norepinephrine Reuptake Inhibitor |
| SARI | Serotonin Antagonist and Reuptake Inhibitors |
| BDNF | Brain-Derived Neurotrophic Factor |
| SD | Standard Deviation |
| MS | Microsoft |
| UK | United Kingdom |
| US | United States |

| | |
|---|---|
| PICAR | Population, Interventions, Comparators, Attributes, and Recommendations |
| $ED_{50}$ | Effective Dose 50 (the dose corresponding to 50% of maximum occupancy) |
| Mg | Milligram |
| RoI | Region of Interest |
| NA | Not available |
| ng/mL | Nanograms per milliliter |
| 5-HT | 5-hydroxytryptamine receptors |
| GABA | Gamma-aminobutyric acid |
| PROSPERO | International Prospective Register of Systematic Reviews |
| HDRS-17 | Hamilton Depression Rating Scale-17 |
| MADRS | Montgomery-Asberg Depression Rating-Scale |

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## The three articles

REVIEW ARTICLE OPEN

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# The relationship between dose and serotonin transporter occupancy of antidepressants—a systematic review

Anders Sørensen[1✉], Henricus G. Ruhé[2,3] and Klaus Munkholm[4,5]



Brain imaging techniques enable the visualization of serotonin transporter (SERT) occupancy as a measure of the proportion of SERT blocked by an antidepressant at a given dose. We aimed to systematically review the evidence on the relationship between antidepressant dose and SERT occupancy. We searched PubMed and Embase (last search 20 May 2021) for human in vivo, within-subject PET, or SPECT studies measuring SERT occupancy at any dose of any antidepressant with highly selective radioligands ([$^{11}$C]-DASB, [$^{123}$I]-ADAM, and [$^{11}$C]-MADAM). We summarized and visualized the dose-occupancy relationship for antidepressants across studies, overlaying the plots with a curve based on predicted values of a standard 2-parameter Michaelis–Menten model fitted using the observed data. We included seventeen studies of 10 different SSRIs, SNRIs, and serotonin modulators comprising a total of 294 participants, involving 309 unique occupancy measures. Overall, following the Michaelis–Menten equation, SERT occupancy increased with a higher dose in a hyperbolic relationship, with occupancy increasing rapidly at lower doses and reaching a plateau at approximately 80% at the usual minimum recommended dose. All the studies were small, only a few investigated the same antidepressant, dose, and brain region, and few reported information on factors that may influence SERT occupancy. The hyperbolic dose-occupancy relationship may provide mechanistic insight of relevance to the limited clinical benefit of dose-escalation in antidepressant treatment and the potential emergence of withdrawal symptoms. The evidence is limited by non-transparent reporting, lack of standardized methods, small sample sizes, and short treatment duration. Future studies should standardize the imaging and reporting procedures, measure occupancy at lower antidepressant doses, and investigate the moderators of the dose-occupancy relationship.

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## INTRODUCTION

Many antidepressants are defined by their high affinity for the serotonin transporter (SERT). Brain imaging studies using positron emission tomography (PET) and single photon emission computed tomography (SPECT) techniques have enabled the in vivo visualization of neurotransmitter receptor occupancy, and thus of the proportion of SERT blocked, at a given dose of a drug. By using radioligands that bind to the available SERT receptors, PET and SPECT techniques provide an estimate of the expression of SERT in a particular brain region, usually given as the non-displaceable binding potential ($BP_{ND}$)—the ratio of the specifically bound radioligand to that of non-displaceable radioligand. When antidepressants with an affinity for SERT are administered, the SERT availability for binding of the radioligand decreases, depending on the binding of the antidepressant to SERT. By visualizing the binding potential in the drug free state and subsequently after administration of an antidepressant, PET and SPECT imaging can provide an estimate of the antidepressant occupancy of SERT.

As one postulated working mechanism of many antidepressants is serotonin reuptake inhibition via blockade of SERT [1], PET and SPECT imaging studies may potentially provide mechanistic insight into important clinical aspects of antidepressant treatment relevant to both the effectiveness of the treatment but also symptoms that may arise during tapering or discontinuation of the treatment. The efficacy of antidepressant treatment for depression is modest compared with placebo [2, 3] and many patients may need additional treatment or treatment adjustments. Common treatment strategies in patients with depression for whom antidepressant treatment has not been effective include increasing the antidepressant dose or switching to a different antidepressant; such strategies may, however, also largely be ineffective [4–7]. Although a relation between SERT occupancy and clinical improvement in depressive symptoms has not been shown [1], knowledge about the relationship between antidepressant dose and SERT occupancy, as well as overlapping actions on SERT between different antidepressants, may be able to provide some mechanistic insight into the apparently limited effectiveness of the above treatment strategies. Approximately half of the patients stopping or reducing the dose of antidepressants experience withdrawal symptoms [8], which, among others, may include flu-like symptoms, anxiety, emotional lability, lowering of mood, and irritability [9, 10]. As one postulated

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mechanism underlying antidepressant withdrawal symptoms is a rapid decrease in SERT occupancy arising when antidepressants are tapered or stopped [11, 12], a clearer understanding of the SERT occupancy at specific, especially lower, doses may provide essential mechanistic information for understanding the occurrence of withdrawal symptoms. Given the paucity of evidence for specific tapering regimens [13, 14], this could perhaps offer insights into better approaches to mitigate withdrawal symptoms. The potential utility of the dose/occupancy relationship in guiding tapering to mitigate withdrawal symptoms has received recent interest by multiple groups [11, 12, 15], and was considered in a recent Cochrane review on approaches to antidepressant discontinuation [14] and in a recent iteration of a major guideline on the management of patients with mood disorders [16].

While several individual studies have investigated the relationship between dose and SERT occupancy of antidepressants [17–19], this evidence has not been systematically reviewed, which we, therefore, aimed to do. Our primary objective was to determine the relationship between the dose and SERT occupancy measured with highly selective radioligands for antidepressants. In studies that repeated measurements of SERT occupancy over time after discontinuation, we additionally aimed to determine the SERT occupancy decline rate and relate it to the plasma concentration decline rate.

## METHODS

We conducted a systematic review of in vivo PET and SPECT studies that measured SERT occupancy of antidepressants in humans using a within-subject design. We registered a protocol at the Open Science Framework before undertaking the review, which can be accessed at: https://osf.io/b6hau/. We reported the review according to the PRISMA guidelines [20].

### Search strategy and selection criteria

Studies investigating SERT occupancy at any given dose of any approved antidepressant administered orally in humans were eligible. We included studies using the ligands [$^{11}$C]-DASB, [$^{123}$I]-ADAM, and [$^{11}$C]-MADAM, which all have a 1000:1 affinity for SERT over the dopamine transporter (DAT) and the norepinephrine transporter (NET) [21, 22]. In addition, these ligands have all been extensively validated via kinetic modeling of arterial input sampling [23–26]. We excluded studies using the ligands [$^{11}$C](+)-McN and [$^{123}$I]-ß-CIT due to their non-selectivity for SERT over other receptors: [$^{123}$I]-ß-CIT has nearly equal affinity for SERT and DAT, while [$^{11}$C](+)-McN is considered "likely selective" with an affinity for SERT over NET of between 10:1 and 100:1 [21]. We considered studies using a within-subject design only, not studies using a between-subject design, as our focus was occupancy, which is optimally calculated in a within-subject design; the study design minimizes variance and is, therefore, more likely than a between-subject design to provide reliable estimates of the relationship between antidepressant dose and occupancy.

We searched PubMed and Embase (last search 20 May 2021). The search terms for Embase were: antidepressant.mp. or exp antidepressant agent/ OR (antidepressant* or SSRI or SNRI or "selective serotonin reuptake inhibitor*" or TCA or tricyclic* or "serotonin-norepinephrine reuptake inhibitor*").af. AND exp serotonin transporter/ AND (occupancy or "binding potential" or availabilit* or block* or chang* or inhibit* or binding ratio or reduc* or quantific* or alter*).af. AND (PET.mp. or exp positron emission tomography/ + SPECT.mp. or exp single photon emission computed tomography/). The search strategy for PubMed is available in the study protocol. In addition to electronic searches, we scanned the references of retrieved articles and relevant review articles.

### Study selection process

Titles and abstracts were screened for eligibility by two researchers independently (AS and KM). Full-text versions of potentially eligible titles were retrieved and read by two researchers independently (AS and KM). Reasons for exclusion were noted. Disagreements were resolved by discussion, which, in case of unresolved issues, involved a third researcher.

### Data items and data extraction

Data were extracted by two researchers independently using a standardized and piloted extraction form. We extracted the following data items: author, year, antidepressant name, antidepressant dose, occupancy, brain region, antidepressant plasma- or serum concentration, $ED_{50}$, duration of intake of the antidepressant, time lag between administration of last dose and time of scanning, type of scan, ligand, method used to quantify SERT binding potential, characteristics of the study (availability of a study protocol, assessment of drug adherence, time of day of scan, fasting regimen used), and characteristics of the participants (age, sex, diagnosis, smoking status, alcohol use, and other medications used).

We contacted study authors whenever data was not available in the articles. When study authors did not reply to supply the data, we extracted it from graphs where possible using a web plot digitizer. This was needed in one study [17].

### Data synthesis

We described the study characteristics and presented key study characteristics in tables. We assessed, for each study, several factors that may affect the relationship between antidepressant dose and occupancy. These were specification of dosing regimen (duration, dose, assessment of adherence, time of last intake), standardization of laboratory methods (time of day, fasting regimen, precision of scanning results, lag time between dose administration and scanning), clinical characterization of participants (clinical diagnosis, age, gender, co-medication, smoking, alcohol use), method used to quantify binding potential, use of reference region, and the type of radioligand.

In our protocol, we planned to conduct a meta-analysis of occupancy data for each drug and dose and to report the summary mean occupancy (with 95% confidence interval) by presenting the summary estimates of occupancy as a function of dose in graphs for each drug and brain region, provided the studies were sufficiently similar. However, too few studies investigated the same drug, brain region, and dose using the same ligand, design, and duration of drug-intake to make a meta-analysis meaningful. We, therefore, presented occupancy for each dose, drug, and brain region in tables as means and standard deviations (SDs).

We visualized the dose-occupancy relationship by plotting occupancy against dose for antidepressants that were administered at four or more different doses across studies; if several occupancy measures were available per study, we prioritized, those with the shortest lag time between administration of the last dose of the antidepressant and imaging and those with the longest antidepressant treatment duration. Based on those data, to provide a visual reference for the data points, we fitted a 2-parameter Michaelis–Menten model implemented by the drm R package using the formula

$$f(x, K, V_m) = \frac{V_m x}{K + x}$$

where $V_m$ is the horizontal asymptote (expressing maximum occupancy), x is the drug dose and the parameter K is the dose where the occupancy is halfway between 0 and $V_m$ [27]. For these models, the lowest dose and occupancy were fixed at 0 and the maximum dose at the highest dosing in any of the included studies. We then plotted the predicted dose-occupancy curve from the model as an overlay to the data plots of occupancy and dose.

In our protocol, we planned to investigate the time-course of the occupancy decline rate as it relates to the antidepressant plasma concentration decline rate, after taking the last dose, by calculating pooled correlation coefficients from the studies that

measured occupancy at several different time points. However, for any drug and dose, no more than one study provided such data, and a meta-analysis was therefore not possible. We, therefore, presented those data narratively instead.

## RESULTS

Our literature search identified 793 abstracts. Screening of titles and abstracts identified 100 records for which we obtained a full-text report. After further removing duplicates ($N = 16$), excluding review articles ($N = 5$), studies not measuring SERT occupancy by antidepressants ($N = 23$), studies administering the drug intravenously ($N = 4$), an animal study ($N = 1$), studies using a between-subjects design ($N = 4$), studies using the non-selective ligands [$^{11}$C](+)-McN or [$^{123}$I]-ß-CIT ($N = 20$), studies of drugs not approved for use in depression or that have been withdrawn ($N = 8$), and studies not providing occupancy expressed as a mean ($N = 3$), a total of 16 articles (reporting on 17 unique studies) were included [17–19, 28–40]. In one article [29], outcomes and methods were elaborated in two other publications [41, 42], which we included accordingly. PRISMA flowchart of study selection process is available in Supplementary Figure 1. Excluded studies, with reasons, are available in Supplementary Table 1.

We contacted the authors of 12 articles to obtain missing data, four of whom were able to provide the requested data [31, 33, 35, 38] (previously unreported data is marked (†) in the tables).

The 17 studies investigated 10 different antidepressants using three different ligands ([$^{11}$C]-DASB ($N = 11$), [$^{11}$C]-MADAM ($N = 2$), and [$^{123}$I]-ADAM ($N = 4$)) and comprised a total of 294 participants (Table 1). In two studies the participants participated in two different scans at different doses after a washout period [30, 33], resulting in a total of 309 unique measurements of occupancy.

The designs of the studies investigated were highly heterogeneous, involving 16 different regions of interest, 11 different durations of drug-intake, 15 different periods of time lag between administration of last dose and time of scanning, two different health statuses (depressed patients or healthy controls), and four different modeling-approaches. An arterial input function was used in one study [33]. The included studies also varied in duration of drug-intake after the (drug-free) baseline scan until imaging of the drug-occupancy, with six studies administering the drug just once and 10 studies using a repeated dose regimen (ranging from 4 days to 10 weeks).

All included studies controlled for adherence to the antidepressant used in the study by measuring plasma- or serum concentrations. Nine of the included studies provided no information on whether participants were taking other drugs and stated no such restrictions to study entry. Eight studies excluded participants taking other possibly interacting medications (e.g., other psychotropic drugs or substances with high affinity for SERT) [19, 31, 32, 37–40, 42]. A fasting regimen was mentioned in one study [35]: requiring a minimum of 4 h fasting prior to imaging. Two studies mentioned having standardized the time of day of drug administration and scanning [19, 35]. One study reported overall alcohol consumption during the study period [35], and seven studies controlled for present or past alcohol problems or abuse [17, 28, 30, 33, 34, 39, 40]. Five of 17 studies included non-smokers only, while the remaining studies did not mention smoking status [19, 30, 35, 39, 40]. None of the studies provided information on a pre-published study protocol.

SERT occupancy of escitalopram was investigated in 55 participants (six studies) [18, 19, 30, 31, 35, 36], citalopram in 77 participants (eight studies) [17–19, 31, 34, 36–38], vortioxetine in 46 participants (two studies presented in one article) [41], paroxetine in 27 participants (three studies) [17, 30, 32], duloxetine in 25 participants (two studies) [28, 40], sertraline in 18 participants (two studies) [17, 30], venlafaxine in 18 participants (one study) [17], fluoxetine in 18 participants (one study) [17], desvenlafaxine in 8 participants (one study) [33], and fluvoxamine in six participants (one study) [39].

Occupancy at different doses and brain regions is presented in Table 2 as the range of means (SD) for each drug. Four studies calculated and reported the dose corresponding to 50% of maximal occupancy ($ED_{50}$). $ED_{50}$ values in mg were 3·4 for citalopram [17], 9·1 for sertraline [17], 5 for paroxetine [17], 2·7 for fluoxetine [17], 5·8 for venlafaxine [17], 7·9 for duloxetine [40], 8·5 for vortioxetine [42], and 14·4 for desvenlafaxine [33]. Figure 1 illustrates the dose-occupancy relationship for antidepressants that were administered at four or more different doses (citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, paroxetine, venlafaxine, and vortioxetine). The relationship between dose and SERT occupancy was fitted according to a 2-parameter Michaelis–Menten model for all antidepressants separately: occupancy increased hyperbolically with increasing antidepressant dose in the lower dose-range, reaching a plateau at an occupancy of approximately 80% at roughly the usual minimum recommended dose for depression (Fig. 1). The relationship between dose and occupancy appeared largely similar across drugs (Fig. 1). For desvenlafaxine and escitalopram, the relationship between dose and occupancy appeared relatively consistent across brain regions; only for escitalopram, the plateau appeared to be reached at a slightly lower occupancy in the putamen, compared with other brain regions, as shown in Table 2 and Fig. 1. The parameter estimates for the Michaelis–Menten model for each antidepressant and brain region of interest (RoI) are provided in Supplementary Table 2.

Five studies provided data on the time-course of SERT occupancy as it decreases over time after a single dose [30, 35, 39, 40] or repeated (7–10 days) [36, 40] administration of antidepressants in healthy volunteers. Three of these studies compared the decline rates of occupancy and plasma concentration (Fig. 2) [30, 36, 39]. For escitalopram [30], citalopram [36], and sertraline [30], but not paroxetine [30] and fluvoxamine [39], SERT occupancy appeared to decrease at a slower rate than the plasma concentration (Fig. 2).

Three studies measured occupancy after both single and repeated dosing in the same subjects [28, 31, 41], all of which showed increased occupancy after repeated dosing compared with a single dose. For duloxetine at 20 mg, occupancy increased from 65% to 78% after four days [28]. For citalopram at 20 mg and escitalopram at 10 mg, occupancy increased from 73% and 74% to 80% and 77%, respectively, after 25 days [31]. For vortioxetine at 2·5, 10, and 60 mg, occupancy increased from 27%, 44%, and 70%, to 35%, 63%, and 93%, respectively, after nine days [41].

## DISCUSSION

For this first systematic review of the evidence of the relationship between dose and SERT occupancy of antidepressants we identified 17 studies investigating 10 different SSRIs, SNRIs and serotonin modulators in a total of 294 participants, comprising 309 unique measurements of SERT occupancy with highly specific ligands. Overall, occupancy increased with higher dose but in a hyperbolic pattern: occupancy increased rapidly at lower doses and reached an apparent plateau at approximately 80%––at the usual minimum recommended dose––modeled by the Michaelis–Menten equation. Generally, the studies were small, only a few studies investigated the same antidepressant at the same dose and in the same RoI, and few studies reported information on relevant factors that may influence drug metabolization and hence bioavailability of antidepressants (e.g. use of potentially interacting drugs, smoking status [43], and alcohol consumption [44]).

The Michaelis–Menten curves we reconstructed based on the findings in individual studies showed that overall, there was no substantial increase of SERT occupancy with SSRI and SNRI doses above the usual minimum recommended doses for depression.

**Table 1.** Study characteristics of included studies.

| Study | Drug | *N* | Total *N* males | Dose range (mg) | Ligand | Lag (hours) | Duration (days) | Age (mean ± SD years) | Diagnosis | RoI | Ref. model |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Meyer et al. (2004) [17] | Cit | 18 | NA[a] | 1–60 | DASB | 6–13 | 28 | NA[a] | Mix of healthy and MDD[b] | Str, BT, ACC, PFC, mid, BC | Logan |
| | Ven | 18 | | 2.4–225 | | | | | | | |
| | Flu | 18 | | 1–60 | | | | | | | |
| | Ser | 14 | | 10–200 | | | | | | | |
| | Par | 14 | | 5–60 | | | | | | | |
| Klein et al. (2006) [18] | Cit | 10 | 20 | 10–20 | ADAM | 6 | 1 | NA[c] | Healthy | Mid | SRTM |
| | Esc | 15 | | 5–20 | | | | | | | |
| Lundberg et al. (2007) [19] | Cit | 8 | 16 | 20 | MADAM | 6 | 1 | NA | Healthy | ACC, FC, TC, ins, hip, put, rap | SRTM |
| | Esc | 8 | | 10 | | | | | | | |
| Baldinger et al. (2014) [31] | Cit | 9 | 6 | 20 | DASB | 6 | 1 + 25 | 42.3 ± 7.8 | MDD | Accu, ins, amy, cau, put, tha, str, mid | MRTM2 |
| | Esc | 10 | | 10 | | | | | | | |
| Klein et al. (2007) [36] | Cit | 9 | 9 | 20 | ADAM | 6 + 54 | 10 | 28 ± 3 | Healthy | Mid | SRTM |
| | Esc | 6 | | 10 | | | | | | | |
| Smith et al. (2011) [38] | Cit | 7 | 4 | 20–40 | DASB | NA | 56–70 | 65 ± 5 | MDD | Str, tha | Logan, MRTM2 |
| Houle et al. (2000) [34] | Cit | 3 | NA | 40 | DASB | 3 | 1 | NA | Healthy | Str, mid, tha | NA |
| Herold et al. (2006) [37] | Cit | 13 | 11 | 10 | ADAM | 6–7 | 7 | NA | MDD | Mid | Logan |
| Kim et al. (2017) [35] | Esc | 12 | 12 | 5–30 | DASB | 3 + 24 + 46 | 1 | 23 ± 2.7 | Healthy | Put, DRN, cau, tha | MRTM2 |
| Arakawa et al. (2016) [30] | Esc | 8 | 8 | 10–20 | DASB | 4 + 24 + 48 | 1 | 29.1 ± 4.6 | Healthy | Tha | SRTM |
| | Ser | 4 | | 50 | | | | | | | |
| | Par | 4 | | 20 | | | | | | | |
| Catafau et al. (2006) [32] | Par | 9 | NA[d] | 20 | ADAM | NA | 39 | NA | MDD | Mid, tha, str | Tissue ratio method |
| Takano et al. (2006a) [39] | Flv | 6 | 6 | 50 | DASB | 5 + 26 + 53 | 1 | 24.3 ± 4.8 | Healthy | FC, tha, str, hip, amy | MRTM2 |
| Takano et al. (2006b) [40] | Dul | 15 | 15 | 5–60 | DASB | 6 + 25 + 49 + 53 + 78 | 1 + 7 | 24.1 ± 2.4 | Healthy | Tha | MRTM2 |
| Abanades et al. (2011) [28] | Dul | 10 | 10 | 20 | DASB | 6, 4 | 1 + 4 | 40.2 ± 11 | Healthy | Mid, str, tha | SRTM |
| Areberg et al. (2012) [41] | Vor | 35 | 35 | 2.5–20 | DASB | 7 | 13 | NA[a] | Healthy | Rap | SRTM |
| Areberg et al. (2012) [41, 42] | Vor | 11 | 11 | 2.5–60 | MADAM | 7 | 1 + 9 | NA[a] | Healthy | Rap | SRTM |
| Frankle et al. (2018) [33] | Des | 15 | 8 | 25–150 | DASB | 24[e] | 3 | 27 ± 9 | Healthy | Mid, tha, amy, str | SRTM |

*N* number of participants, *lag (hours)* time lag in hours between drug administration and scanning, *SD* standard deviation, *RoI* brain region of interest, *Ref. model* reference model for quantifying binding potential, *cit* citalopram, *ven* venlafaxine, *flu* fluoxetine, *ser* sertraline, *par* paroxetine, *esc* escitalopram, *flv* fluvoxamine, *dul* duloxetine, *vor* vortioxetine, *des* desvenlafaxine, *NA* not applicable, *MDD* major depressive disorder, *str* striatum, *BT* bilateral thalamus, *ACC* anterior cingulate cortex, *PFC* prefrontal cortex, *mid* midbrain, *BC* bilateral cuneus, *FC* frontal cortex, *TC* temporal cortex, *ins* insula, *hip* hippocampus, *put* putamen, *rap* raphe nuclei, *accu* accumbens, *amy* amygdala, *tha* thalamus, *cau* caudate, *DRN* dorsal raphe nucleus, *SRTM* simplified reference tissue model, *MRTM-2* multilinear reference tissue model 2.

[a]Information on sex and age provided only for 77 of 82 participants in Meyer 2004 (33 females, 44 males, mean age (SD) 35 (9), and only for both groups combined in Areberg 2012 (46 males, mean age 28 years (21–41).

[b]Healthy participants received low doses, unhealthy participants received high doses.

[c]Mean age data includes four dropouts (26.8 years for all 29 participants).

[d]Participant characteristics include one dropout (6 males, 4 females, mean age (SD) 36 (10.8), range 20–53).

[e]Unique to this review

**Table 2.** Serotonin transporter occupancy at different antidepressant doses.

| Dose in mg | N | RoI (number of occupancy measures) | Occupancy (mean ± SD) | Duration of drug-intake (days) |
|---|---|---|---|---|
| Citalopram | | | | |
| 1 (17) | 2 | str (2) | 16 ± 6% | 28 |
| 2.5 (17) | 2 | str (2) | 42 ± 1% | 28 |
| 5 (17) | 2 | str (2) | 67 ± 18% | 28 |
| 10 (17, 18, 37) | 21 | overall | 61–76 ± 9% | |
| | | str (3) | 76 ± 9% | 28 |
| | | mid (22) | 61–65 ± 10% | 7, 1 |
| 20 (17–19, 31, 36, 38) | 39 | overall | 64 ± 13–91 ± 5 | |
| | | str (17) | 74 ± 5–77 ± 10 | 1, 28 |
| | | mid (23) | 64 ± 13–86 ± 4 | 10, 25 |
| | | ACC (17) | 75 ± 16–80 ± 21 | 1, 25 |
| | | FC (8) | 75 ± 14 | 1 |
| | | TC (8) | 66 ± 19 | 1 |
| | | ins (17) | 71 ± 12–73 ± 9 | 25, 1 |
| | | hip (8) | 78 ± 17 | 1 |
| | | put (17) | 68 ± 5–76 ± 4 | 1, 25 |
| | | rap (8) | 76 ± 9 | 1 |
| | | amy (9) | 91 ± 5 | 25 |
| | | cau (9) | 80 ± 5 | 25 |
| | | tha (13) | 74 ± 7–77 ± 6 | 56–70, 25 |
| | | accu (9) | 84 ± 4 | 25 |
| 30 (38)† | 1 | overall | 67–70 | |
| | | str (1) | 67 | 56–70 |
| | | tha (1) | 70 | 56–70 |
| 40 (17, 34, 38)[a] | 6 | overall | 80 ± 5–85 ± 4 | |
| | | str (8) | 73 ± 6–85 ± 4 | 56–70, 28 |
| | | mid (3) | 80 ± 5 | 1 |
| | | tha (5) | 80 ± 7–80 ± 5 | 56–70, 1 |
| 60 (17) | 2 | str (2) | 87 ± 6 | 28 |
| Escitalopram | | | | |
| 5 (18, 35)[a] | 9 | overall | 50 ± 1–67 ± 7 | |
| | | mid (5) | 60 ± 6 | 1 |
| | | put (4) | 51 ± 1 | 1 |
| | | DRN (4) | 56 ± 2 | 1 |
| | | cau (4) | 67 ± 7 | 1 |
| | | tha (4) | 50 ± 1 | 1 |
| 10 (18, 19, 30, 31, 35, 36) | 37 | overall | 59 ± 5–88 ± 9 | |
| | | mid (20) | 64 ± 6–81 ± 5 | 1, 10 |
| | | ACC (18) | 65 ± 11–75 ± 8 | 1, 25 |
| | | FT (8) | 67 ± 12 | 1 |
| | | TC (8) | 63 ± 23 | 1 |
| | | ins (18) | 59 ± 15–69 ± 9 | 1, 25 |
| | | hip (8) | 59 ± 23 | 1 |
| | | put (22) | 59 ± 5–72 ± 4 | 1, 25 |
| | | rap (8) | 69 ± 13 | 1 |
| | | amy (10) | 88 ± 9 | 25 |
| | | cau (14) | 69 ± 5–78 ± 4 | 1, 25 |
| | | tha (18) | 60 ± 3–75 ± 4 | 1, 25 |
| | | str (10) | 73 ± 4 | 25 |
| | | accu (10) | 81 ± 4 | 25 |
| | | DRN (4) | 74 ± 8 | 25 |
| 20 (18, 30, 35)[a] | 10 | Overall | 65–81 | |
| | | mid (5) | 75 ± 5 | 1 |
| | | put (1) | 65 | 1 |
| | | DRN (1) | 81 | 1 |
| | | cau (1) | 77 | 1 |
| | | tha (5) | 72–78 ± 3 | 1, 1 |
| 30 (35)[a] | 3 | overall | 62 ± 3–79 ± 6 | |
| | | put (3) | 62 ± 3 | 1 |
| | | DRN (3) | 79 ± 6 | 1 |
| | | cau (3) | 71 ± 11 | 1 |
| | | tha (3) | 64 ± 7 | 1 |
| Sertraline | | | | |
| 10 (17) | 3 | str (3) | 49 ± 13 | 28 |
| 25 (17) | 2 | str (2) | 72 ± 4 | 28 |
| 50 (17, 30) | 7 | overall | 74 ± 6–85 ± 7 | 1, 28 |
| | | str (3) | 85 ± 7 | 28 |
| | | tha (4) | 74 ± 6 | 1 |
| 100 (17) | 4 | str (4) | 86 ± 3 | 28 |
| 150 (17) | 1 | str (1) | 87 | 28 |
| 200 (17) | 1 | str (1) | 84 | 28 |
| Paroxetine | | | | |
| 5 (17) | 2 | str (2) | 52 ± 16 | 28 |
| 10 (17) | 1 | str (1) | 60 | 28 |
| 20 (17, 30, 32) | 21 | overall | 45 ± 21–93 ± 8 | |
| | | str (17) | 61 ± 11–82 ± 10 | 39, 28 |
| | | BT (7) | 75 ± 16 | 28 |
| | | ACC (7) | 76 ± 15 | 28 |
| | | PFC (7) | 80 ± 18 | 28 |
| | | tha (13) | 45 ± 21–63 ± 10 | 1, 39 |
| | | mid (16) | 66 ± 10–93 ± 8 | 39, 28 |
| | | BC (7) | 67 ± 29 | 28 |
| 40 (17) | 2 | str (2) | 90 ± 2 | 28 |
| 60 (17) | 1 | str (1) | 91 | 28 |
| Fluoxetine | | | | |
| 1 (17) | 2 | str (2) | 30 ± 6 | 28 |
| 2.5 (17) | 2 | str (2) | 41 ± 13 | 28 |
| 4 (17) | 1 | str (1) | 67 | 28 |
| 5 (17) | 2 | str (2) | 65 ± 6 | 28 |
| 10 (17) | 2 | str (2) | 73 ± 1 | 28 |
| 20 (17) | 4 | overall | 69 ± 9–85 ± 9 | 28 |
| | | str (4) | 76 ± 8 | 28 |
| | | BT (4) | 69 ± 9 | 28 |
| | | ACC (4) | 80 ± 14 | 28 |
| | | PFC (4) | 85 ± 9 | 28 |
| | | mid (4) | 82 ± 9 | 28 |
| | | BC (4) | 81 ± 6 | 28 |
| 40 (17) | 4 | str (4) | 83 ± 9 | 28 |
| 60 (17) | 1 | str (1) | 82 | 28 |
| Fluvoxamine | | | | |
| 50 (39) | 6 | overall | 71 ± 2–76 ± 3 | |
| | | FC (6) | 75 ± 9 | 28 |
| | | tha (6) | 72 ± 4 | 28 |
| | | str (6) | 71 ± 2 | 28 |
| | | hip (6) | 76 ± 3 | 28 |
| | | amy (6) | 72 ± 13 | 28 |
| Venlafaxine | | | | |
| 2.4 (17) | 2 | str (2) | 25 ± 13 | 28 |
| 5 (17) | 2 | str (2) | 40 ± 1 | 28 |
| 10 (17) | 1 | str (1) | 63 | 28 |
| 18.75 (17) | 2 | str (2) | 66 ± 3 | 28 |
| 37.5 (17) | 3 | str (3) | 76 ± 10 | 28 |
| 75 (17) | 4 | overall | 71 ± 10–92 ± 5 | 28 |
| | | str (4) | 84 ± 2 | 28 |
| | | BT (4) | 71 ± 10 | 28 |
| | | ACC (4) | 85 ± 13 | 28 |

**Table 2** continued

| Dose in mg | *N* | RoI (number of occupancy measures) | Occupancy (mean ± SD) | Duration of drug-intake (days) |
|---|---|---|---|---|
| | | PFC (4) | 91 ± 11 | 28 |
| | | mid (4) | 91 ± 8 | 28 |
| | | BC (4) | 92 ± 5 | 28 |
| 150 (17) | 2 | str (2) | 90 ± 1 | 28 |
| 225 (17) | 2 | str (2) | 87 ± 4 | 28 |
| Duloxetine | | | | |
| 5 (40) | 3 | tha (3) | 44 ± 9 | 1 |
| 20 (28, 40) | 13 | overall | 71 ± 5–85 ± 4 | |
| | | tha (13) | 71 ± 5–74 ± 7 | 1, 4 |
| | | mid (10) | 85 ± 4 | 4 |
| | | str (10) | 75 ± 8 | 4 |
| 40 (40) | 3 | tha (3) | 81 ± 5 | 1 |
| 60 (40) | 3 | tha (3) | 85 ± 3 | 7 |
| Vortioxetine | | | | |
| 2.5 (41, 42) | 16 | RN (16) | 35 ± 10–49 ± 12 | 9, 13 |
| 5 (41) | 11 | RN (11) | 51 ± 10 | 13 |
| 10 (42) | 4 | RN (4) | 63 ± 23 | 9 |
| 20 (41) | 12 | RN (12) | 90 ± 6 | 13 |
| 60 (42) | 3 | RN (3) | 93 ± 9 | 9 |
| Desvenlafaxine | | | | |
| 25 (33) | 4 | overall | 55 ± 5–71 ± 13 | |
| | | mid (4) | 68 ± 8 | 3 |
| | | tha (4) | 55 ± 5 | 3 |
| | | amy (4) | 71 ± 13 | 3 |
| | | str (4) | 60 ± 7 | 3 |
| 50 (33) | 4 | overall | 70 ± 8–90 ± 9 | |
| | | mid (4) | 85 ± 7 | 3 |
| | | tha (4) | 70 ± 8 | 3 |
| | | amy (4) | 90 ± 9 | 3 |
| | | str (4) | 77 ± 7 | 3 |
| 100 (33) | 3 | overall | 78 ± 2–96 ± 5 | |
| | | mid (3) | 87 ± 6 | 3 |
| | | tha (3) | 78 ± 2 | 3 |
| | | amy (3) | 96 ± 5 | 3 |
| | | str (3) | 87 ± 1 | 3 |
| 150 (33) | 4 | overall | 90 ± 3–97 ± 4 | |
| | | mid (4) | 94 ± 6 | 3 |
| | | tha (4) | 91 ± 10 | 3 |
| | | amy (4) | 97 ± 4 | 3 |
| | | str (4) | 90 ± 3 | 3 |

Where a dose was only investigated in one study, the mean (SD) occupancy of that individual study is presented; where a dose was investigated in multiple studies, the range of means (SD) from those studies is presented. Duration of drug-intake for the individual studies is presented in the same order as the occupancy range.
*N* number of participants, *RoI* brain region of interest (number of occupancy measures in the different regions), *SD* standard deviation, *str* striatum, *mid* midbrain, *ACC* anterior cingulate cortex, *FC* frontal cortex, *TC* temporal cortex, *ins* insula, *hip* hippocampus, *put* putamen, *rap* raphe nuclei, *amy* amygdala, *cau* caudate, *tha* thalamus, *accu* accumbens, *DRN* dorsal raphe nucleus, *BC* bilateral cuneus.
[a]Full occupancy data is unique to this review.

This finding is in accordance with one dose-escalation occupancy study of paroxetine using the β-CIT, a ligand not included in the present review, that found no increase in SERT occupancy, nor a clinical effect as a result of paroxetine dose escalation from 20 to 50 mg, despite observed increases in paroxetine serum concentration [45]. It is also in agreement with the observation that there is a limited benefit associated with increasing doses of SSRIs above the lower range of the licensed dose in general, whether using a fixed dosing regimen [4, 5], a flexible dosing regimen [46], or as a second-step strategy in patients not responding to standard dosing [6, 45]. Adverse events, in contrast, may have an ascending dose-response curve [4, 47], presumably due to co-affinity to other receptors. There is no firm evidence that clinical efficacy [1, 17, 45], nor adverse effects are dependent on SERT occupancy; the studies included in the present review that measured the relationship between clinical effect and SERT occupancy did not find significant correlations [17, 32, 37, 38, 48].

Even at, and below, the lowest manufactured dose of the antidepressants we included, there is considerable SERT occupancy. For all drugs except vortioxetine, 50% occupancy occurred at doses quite below half of the lowest manufactured dose. Given this hyperbolic relationship between dose and SERT occupancy, even relatively small dose changes at the lower dose range will have large effects on SERT occupancy and thus presumably on synaptic serotonin levels—with progressively increasing magnitude as the dose decreases linearly towards zero. This finding may particularly have implications for discontinuation and tapering, as a linear tapering regimen, involving stopping at the lowest manufactured dose, or even half of it would correspond to increasingly larger reductions in occupancy, which might be related to the occurrence of withdrawal symptoms. Assuming that withdrawal symptoms are predominantly related to unblocking of SERT, a linear and gradual unblocking of SERT, which has been suggested to mitigate withdrawal symptoms [11, 45], would require a hyperbolic dose reduction regimen, necessitating smaller dose decrements than possible with currently manufactured antidepressants. Eventually, this assumption should be tested in a blinded RCT, where the primary hypothesis would be that discontinuation via hyperbolic tapering should be more successful, with less withdrawal symptoms than stopping via the lowest manufactured dose (or half of it).

Conversely, even large dose reductions above the occupancy plateau appear to be associated with only relatively minor decreases in SERT occupancy, and dose reductions at higher doses may therefore potentially be less likely to result in marked withdrawal symptoms although, similar to the lack of evidence for a relationship with efficacy, there is no unequivocal evidence of a correlation between changes in SERT occupancy and withdrawal symptoms. As SSRIs, SNRIs, and serotonin modulators are not selective to SERT [49–52], dose reductions in the higher dose-range, while not markedly reducing SERT occupancy, could potentially also result in changes in other transmitter systems that could potentially be associated with withdrawal symptoms. However, given that the shape of the receptor occupancy curve is hyperbolic for most dose–response relationships, consequent to the law of mass action [53, 54], hyperbolic dose reduction is likely pharmacologically meaningful regardless of the specific receptor systems contributing to withdrawal symptoms.

The observation that escitalopram, citalopram, and sertraline SERT occupancy appear to decrease at a slower rate compared with the plasma concentration of the drugs may indicate that plasma half-life does not accurately reflect the rate at which SERT occupancy declines. This apparently delayed decrease in SERT occupancy compared with the plasma concentration decline could be speculated to contribute to the delayed withdrawal effects, which have been observed clinically.

Several issues related to the study designs must be taken into consideration when interpreting our findings since these could contribute to the heterogeneity of findings between studies. The included studies that measured occupancy after both single and repeated dosing all found that occupancy increased with longer treatment, the absolute occupancy being in the range of 3 to 23% higher after repeated dosing compared with single dosing [28, 31, 41]. This suggests that occupancy data from single-dose studies may underestimate the occupancy occurring in patients who take the drugs continuously for extended periods. A possible reason

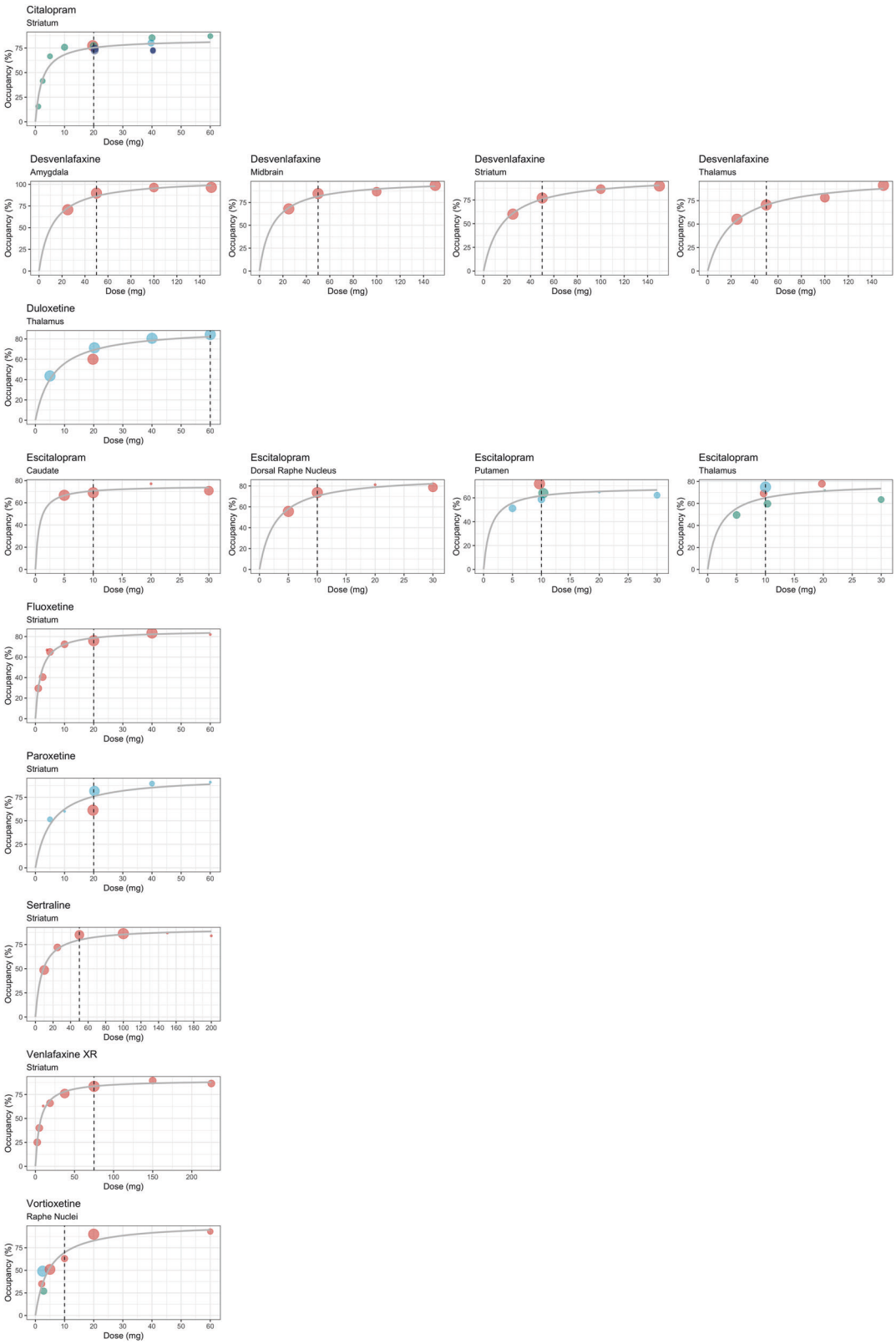


**Fig. 1 Occupancy and dose relationship for antidepressants administered at four or more doses.** The dose-occupancy relationship for antidepressants that were administered at four or more different doses (citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, paroxetine, venlafaxine, and vortioxetine), fitted according to a 2-parameter Michaelis–Menten model as $f(x, K, V_m) = \frac{V_m x}{K+x}$, where $V_m$ is the horizontal asymptote (expressing maximum occupancy), x is the drug dose and the parameter K is the dose where the occupancy is halfway between 0 and $V_m$. The parameter estimates $V_m$ and K for each model are provided in Supplementary Table 2. For each individual figure, studies are represented by uniquely colored dots; the size of the dots is proportional to the number of occupancy measures. Dashed vertical lines represent the usual minimum recommended dose.

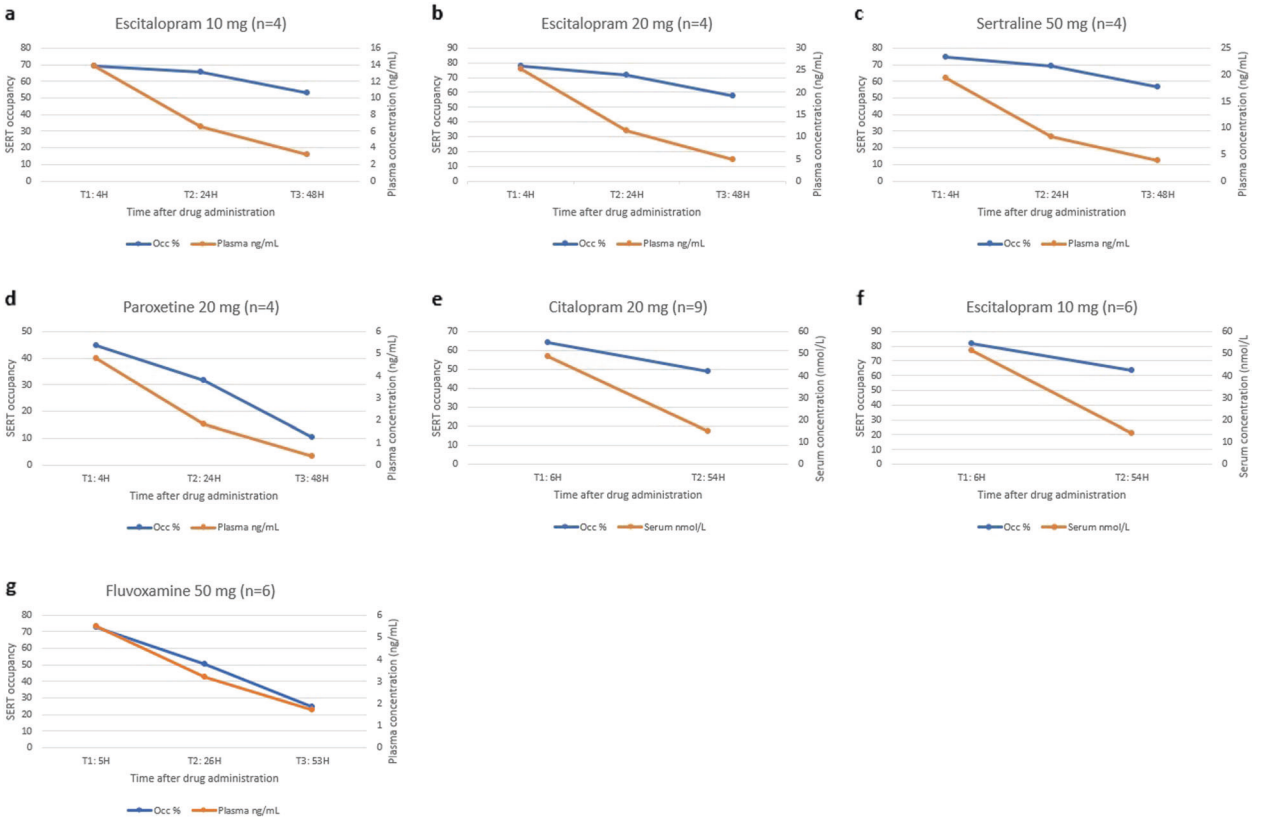


**Fig. 2 Time-course of occupancy and plasma/serum concentration.** The relationship between serotonin transporter occupancy and plasma/serum concentration as it decreases over time after dose administration of escitalopram, citalopram, sertraline, paroxetine, and fluvoxamine. mg milligram, N number of participants, SERT Serotonin transporter, H hours after drug administration, Occ serotonin transporter occupancy, ng/mL nanograms per milliliter, nmol/L nanomoles per litre.

for this finding is that after the first administration of an antidepressant these lipophilic drugs dissolve into the entire body, which only becomes saturated after repeated dosing. Additionally, studies varied in the duration between the last dose administration and time of scanning (ranging from three to 24 h), which could underlie some of the heterogeneity of the observed SERT occupancy, although this is expected to cause less variability after longer treatment when a steady-state of the antidepressant plasma concentration will be established. It is also not clear whether our findings are generalizable to all patients on antidepressants, especially for all ages and both sexes, as most included studies investigated healthy individuals in the age range from 25 to 40 years, of whom most were male. Few studies provided precise information on all factors relevant to measuring occupancy, and accurate participant characteristics were sometimes difficult to determine since some studies included dropouts and later excluded participants when reporting age and sex characteristics. Tobacco smoking [43], alcohol consumption [44], fasting [55], and concomitant drug use [56, 57] may influence antidepressant metabolization and thus the bioavailability of the drugs, which, in turn, could affect the relationship between antidepressant dose and occupancy, but information on those factors was not available in most studies. Sample sizes were generally small; five drugs were investigated in less than 20 participants each, and some doses were investigated in just one to three participants. Consideration should also be given to the fact that PET and SPECT are known to detect signals of unspecific radioligand binding, i.e. noise that does not represent target occupancy. Therefore, a reference region assumed devoid of specific SERT binding must be used as control, assuming that signals detected in this brain region do not represent specific binding to SERT. Cerebellum was earlier suggested as the optimal reference region, but later studies revealed that cerebellum is not completely devoid of specific SERT binding. Therefore, the binding potential will be slightly overestimated if this issue is not specifically controlled for, which only one study did [35]. Since all included studies used cerebellum as reference region, this will have resulted in a small and systematic bias. Finally, occupancies in smaller brain regions, like the amygdala, are likely determined with less certainty compared with larger brain regions due to issues of radiotracer reliability in brain regions that are small relative to the resolution of SPECT.

Our study is the first to review the body of evidence of the relationship between dose and SERT occupancy of antidepressants. This not only provides a complete picture of the evidence across many different antidepressants but also allows for a more detailed assessment of the relationship between dose and SERT occupancy by integrating data from different studies for the same antidepressants. Importantly, it also allowed for an assessment of the limitations in the evidence base. In addition to these strengths, our study has several limitations. First, we presented findings from studies using different reference tissue models together; these could influence occupancy measures. However, one study calculated occupancy using three different methods, and found only minor differences between SRTM, MRTM-2, and logan [38], potentially indicating that the reference tissue model does not substantially bias SERT occupancy. Second, comparison of occupancy data from different brain regions is potentially not meaningful, as SERT is not equally distributed throughout the brain [1]. It is therefore possible that the reported occupancy measures do not reflect those areas which are most important for patients, clinically. Whether blocking of SERT in some brain regions is of particular importance regarding treatment effect, adverse events, or withdrawal symptoms remains

unresolved. Third, our literature search may have missed some studies that did measure occupancy but used different terms due to inconsistent nomenclature for occupancy and binding potential, especially in the field's earlier stages. However, our search strategy was created with this in mind, and we systematically scanned the reference lists of all included studies. Fourth, our plot overlays fitted using the Michalis-Menten model did not consider the sample size of individual studies; an overlay plot based on individual patient data would have been preferable, but we did not obtain those data. Along this line, the dose ranges were limited for some drugs, which means that it is uncertain whether the observed plateau for those drugs at approximately 80% occupancy represents the highest possible level of the plateau, e.g. for escitalopram the highest dose was 30 mg and for duloxetine 60 mg. Lastly, in order to investigate differences in occupancy between single- and repeated dosing regimens, which appear to yield different occupancy levels, we synthesized the evidence using both dosing regimens but due to few studies, it was not possible to construct fitted curves stratified by dosing regimen. Along the same line, we included studies regardless of whether co-medication was allowed, which may have contributed to heterogeneity in results between studies; due to the scarcity of data it was not possible to explore the potential effect of co-medication.

### Implications for future research

Our review points to a need for larger occupancy studies of antidepressants administered also at low doses, investigation of moderators of the dose-occupancy relationship, standardization of methods, assessment of associations with clinical effects, and more transparent reporting. Future studies should also measure other transporters (e.g., NET and DAT) than SERT to uncover the full biological effects of the drugs as many antidepressants also act on non-serotonergic systems. As many patients take antidepressants for years, studies should also study patients (before and) after long treatment duration. Finally, the theoretical link between unblocking of SERT and withdrawal symptoms should ideally be investigated directly, for example by measuring occupancy with repeated measurements during a period of dose reduction while recording the occurrence of potential withdrawal symptoms. The feasibility of conducting such studies, however, would be challenged by likely high costs associated with long follow-up, an unknown event rate, and issues associated with performing repeated PET procedures.

### Conclusion

PET and SPECT studies provide a mechanistic background for understanding the limited effect of dose-escalation of antidepressants and for the potential emergence of withdrawal symptoms even with small dose reductions in the lower dose range. The evidence base is limited by few, small studies of short treatment duration and sub-optimal, non-uniform reporting, which should be improved in the future. Such improvements could lead to a better understanding of factors influencing SERT occupancy and the association with treatment efficacy, adverse effects, and withdrawal symptoms after dose-reductions or stopping of antidepressants.

## DATA AVAILABILITY

All data (including template data collection forms, data extracted from included studies, and data used for all analyses) are available on the Open Science Framework at: https://doi.org/10.17605/OSF.IO/RKYFS.

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## AUTHOR CONTRIBUTORS

All authors contributed to the study. AS and KM planned the project and wrote the research protocol. AS did the literature search and data extraction with KM and Marinos Ioannides as second and independent researchers. AS wrote the first draft of the manuscript with input from KM. HGR contributed to the interpretation of the data and provided extensive critical revisions of the manuscript. All three authors revised the manuscript and approved its final version.

## COMPETING INTERESTS

AS has nothing to disclose. KM has nothing to disclose. HGR reports Speaking Fees from Janssen, grants from ZonMW (GGG), HersenStichting NL, and is Chair of the Multidisciplinary Task-Force Discontinuation Antidepressants and vice-Chair of the Multidisciplinary Guideline for Unipolar Depression in the Netherlands, all outside the submitted work.

## ADDITIONAL INFORMATION

**Supplementary information** The online version contains supplementary material available at https://doi.org/10.1038/s41380-021-01285-w.

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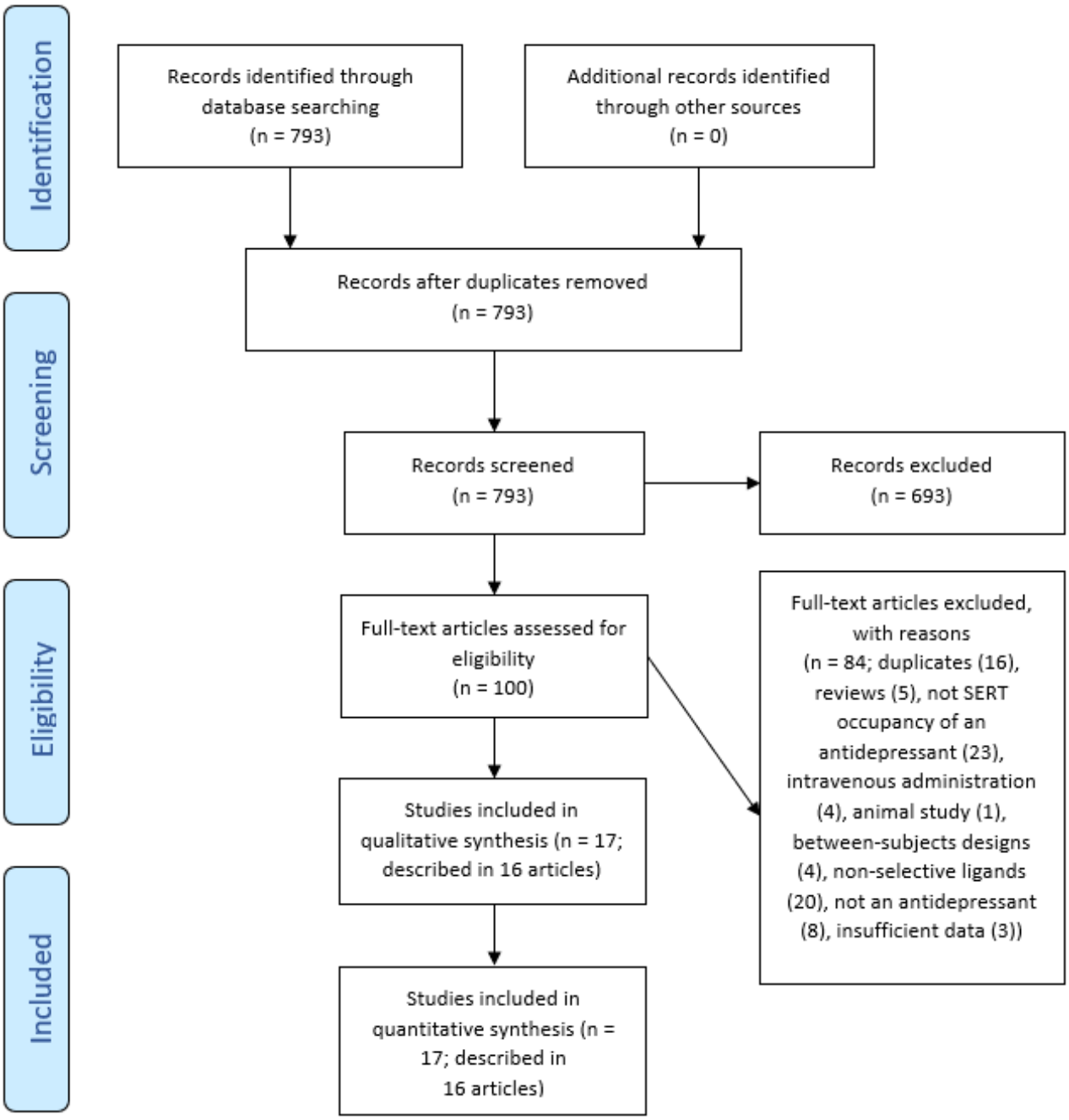
**Supplementary Figure 1.** PRISMA flowchart of study selection process



**Supplementary Table 1.** List of excluded studies with reasons

**Animal studies (N=1)**

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**Supplementary Table 2.** Parameter estimates for the 2-parameter Michaelis-Menten models employed to fit individual curves in Figure 1

| **Antidepressant** | **RoI** | **$V_m$** | **K** |
|---|---|---|---|
| Citalopram | Striatum | 83.98 | 2.33 |
| Desvenlafaxine | Amygdala | 106.43 | 11.57 |
| Desvenlafaxine | Midbrain | 99.46 | 10.92 |
| Desvenlafaxine | Striatum | 100.22 | 16.11 |
| Desvenlafaxine | Thalamus | 100.11 | 21.17 |
| Duloxetine | Thalamus | 90.75 | 6.27 |
| Escitalopram | Caudate | 75.35 | 0.66 |
| Escitalopram | Dorsal Raphe Nucleus | 89.57 | 2.72 |
| Escitalopram | Putamen | 69.32 | 1.22 |
| Escitalopram | Thalamus | 78.67 | 2.10 |
| Fluoxetine | Striatum | 86.12 | 1.89 |
| Paroxetine | Striatum | 97.14 | 5.60 |
| Sertraline | Striatum | 92.01 | 7.72 |
| Venlafaxine XR | Striatum | 90.07 | 5.80 |
| Vortioxetine | Raphe Nuclei | 102.24 | 4.68 |

**Supplementary table 2 legend:** RoI: brain region of interest; Vm: the horizontal asymptote (expressing maximum occupancy); K: the dose where the occupancy is halfway between 0 and $V_m$.

Therapeutic Advances in Psychopharmacology Systematic Review

# Clinical practice guideline recommendations on tapering and discontinuing antidepressants for depression: a systematic review

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***Abstract***

**Background:** Tapering and discontinuing antidepressants are important aspects of the management of patients with depression and should therefore be considered in clinical practice guidelines.

**Objectives:** We aimed to assess the extent and content, and appraise the quality, of guidance on tapering and discontinuing antidepressants in major clinical practice guidelines on depression.

**Methods:** Systematic review of clinical practice guidelines on depression issued by national health authorities and major national or international professional organisations in the United Kingdom, the United States, Canada, Australia, Singapore, Ireland and New Zealand (PROSPERO CRD42020220682). We searched PubMed, 14 guideline registries and the websites of relevant organisations (last search 25 May 2021). The clinical practice guidelines were assessed for recommendations and information relevant to tapering and discontinuing antidepressants. The quality of the clinical practice guidelines as they pertained to tapering and discontinuation was assessed using the AGREE II tool.

**Results:** Of the 21 included clinical practice guidelines, 15 (71%) recommended that antidepressants are tapered gradually or slowly, but none provided guidance on dose reductions, how to distinguish withdrawal symptoms from relapse or how to manage withdrawal symptoms. Psychological challenges were not addressed in any clinical practice guideline, and the treatment algorithms and flow charts did not include discontinuation. The quality of the clinical practice guidelines was overall low.

**Conclusion:** Current major clinical practice guidelines provide little support for clinicians wishing to help patients discontinue or taper antidepressants in terms of mitigating and managing withdrawal symptoms. Patients who have deteriorated upon following current guidance on tapering and discontinuing antidepressants thus cannot be concluded to have experienced a relapse. Better guidance requires better randomised trials investigating interventions for discontinuing or tapering antidepressants.

***Keywords:*** antidepressant tapering, clinical practice guidelines, depression, withdrawal symptoms

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## Introduction

Clinical practice guidelines (CPGs) on depression generally recommend treatment with an antidepressant for moderate to severe episodes of depression as one treatment option and, given the clinical situation, the treatment is recommended to stop after a certain period.[1–3] About half of the patients on antidepressants who try to discontinue or reduce the dose experience withdrawal symptoms,[4,5] including flu-like symptoms, anxiety, emotional lability, lowering of mood, irritability, bouts of crying, dizziness, shaking, fatigue

and electric shock sensations.[6,7] The symptoms usually persist for weeks but can last months or even years,[4] and half of the patients who experience them rate the symptoms as severe.[4] Beyond the physiological effects related to drug withdrawal, discontinuing antidepressants can be difficult for psychological reasons. These include worry of relapse, a perceived biochemical cause of depression, insufficient emotion regulation skills and coping strategies, need for social support, psychological dependence, and experience of previous unsuccessful discontinuation attempts.[8–11]

The incidence and severity of withdrawal symptoms may depend on how the antidepressant is tapered,[12–16] suggesting that the dose-reduction regimen is an important factor to successful discontinuation of antidepressants. Studies thus indicate that short-term tapering regimens result in a lower proportion of patients succeeding in discontinuing antidepressants compared with a longer tapering period.[13–15] Furthermore, preliminary data from non-randomised trials suggest that hyperbolic tapering through tapering strips may reduce the incidence of withdrawal symptoms.[17,18] Some CPGs, however, recommend short periods of tapering or even no tapering at all, depending on the specific antidepressant,[1,2] but the evidence base for such recommendations is unclear.[19,20]

Tapering and discontinuing antidepressants are important aspects of the management of patients with depression, and relevant guidance should be considered an integral part of treatment guidelines for depression. The extent and characteristics of such guidance in current CPGs, however, is unclear.

We thus aimed to, for the first time, systematically review the guidance on tapering and discontinuing antidepressants in CPGs for depression issued by those national health authorities or major national or international professional organisations and societies that are likely to have the most impact on clinical practice. Our primary objective was to assess the extent and content of the guidance on tapering and discontinuing of antidepressants. As a secondary objective, we wished to appraise the quality of these guidelines as they pertained to discontinuation and tapering of antidepressants.

## Methods

We conducted a systematic review of CPGs on depression and appraised their quality using the AGREE II instrument.[21]

Our protocol was developed according to the PRISMA-P guideline[22] and was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 16 November 2020 (registration ID CRD42020220682). We reported the review according to the PRISMA guideline.[23]

### *Eligibility criteria*

We defined the inclusion and exclusion criteria according to the PICAR framework for systematic reviews of CPGs (Table 1).[24]

To ensure clinical relevance, eligibility was restricted to CPGs issued by national health authorities and major national or international professional organisations or societies in English-speaking high-income countries (the United Kingdom, the United States, Canada, Australia, Singapore, Ireland and New Zealand). Thus, we prioritised guidelines with the likely highest impact on clinical practice internationally over the inclusion of all existing treatment guidelines on depression. There were no restrictions on publication year. For each guideline, if several iterations were available, we included the latest version.

We included CPGs for the treatment of depression that recommended antidepressants. CPGs on non-pharmacological treatment only and CPGs that focused on the treatment of conditions other than depression were excluded. We applied no restrictions on symptom severity, treatment duration, comorbidity, other treatments, age, sex, ethnicity or hospitalisation status.

### *Data sources and searches*

We first manually searched the websites of the governmental organisations, national health authorities, national psychiatric societies, and national psychological societies of each country and those of major international professional societies.

Next, we searched PubMed and 14 guideline registries [National Institute for Health and Care Excellence, Standards and Guidelines Evidence, American College of Physicians Clinical Practice Guidelines, National Health and Medical Research Council, New Zealand Guidelines Group, eGuidelines, Guidelines.co.uk, Guidelines International Network Library, Scottish Intercollegate Guidelines Network, the former National Guideline Clearinghouse (now hosted at www.ahrq.gov), Canadian Medical Association Infobase, National

**Table 1.** PICAR inclusion criteria.

| | |
|---|---|
| Population & clinical indication | Patients with depression<br>Any age<br>Any symptom severity |
| Interventions | Antidepressant treatment |
| Comparators, comparisons and content | *Comparators*: Any, including none<br>*Key content*: Guidance on stopping or reducing treatment |
| Attributes of eligible CPGs | *Language*: Available in English<br>*Year of publication*: Most recent from each organisation<br>*Publishing region*: English-speaking, high-income countries<br>*Version*: Latest version only<br>*System of rating evidence*: Any<br>*Scope*: Must have primary focus on treatment of depression<br>*Recommendations*: No restrictions; CPGs will be included regardless of whether they contain guidance on tapering/discontinuation treatment or not |
| Recommendation characteristics | *Duration of treatment*: No restrictions<br>*Levels of confidence*: No restrictions<br>*Interventions*: No restrictions<br>*Comparators*: No restrictions; recommendations are not required to compare an intervention of interest with another intervention<br>*Locating recommendations*: Within CPG text, tables, algorithms or decision paths |

CPG, clinical practice guideline.

Library for Health Guidelines Finder, Best Practice Guidelines, and Magic]. See Supplementary Table 1 for details. Search terms for PubMed were as follows: [Depression(TI) OR 'Depressive Disorder' (Mesh) OR 'Depression'(Mesh)] AND [guideline (Publication Type) OR guideline*(TI)].

Finally, we searched Google for additional unique records using broader search terms for 'depression' and 'guideline', screening the top 100 hits, and scanned the reference lists of all retrieved CPGs.

All sources were last searched on 25 May 2021.

### *Study selection*

Two researchers (A.S. and K.M.) independently screened the titles and abstracts of the identified records for eligibility. Full reports were retrieved for all records that appeared to meet our inclusion criteria or where there was uncertainty and screened for eligibility by two researchers (A.S. and K.M.) independently. Reasons for exclusion were noted. Disagreements were resolved by discussion, potentially involving a third researcher (K.J.J.). For all included CPGs we, additionally, retrieved any associated companion articles (e.g. methodology supplements and background documents) or relevant accompanying online information.

### *Data extraction*

Two researchers (A.S. and K.M.) read the guideline documents and independently extracted the data using a standardised and piloted data extraction form in MS Excel™. Disagreements were resolved by discussion. We extracted the following data: title, year, source, country of origin, authors, funding source, conflicts of interest, when to consider discontinuing antidepressants, duration of maintenance treatment, duration of tapering period, dose-reduction regimen, tapering regimen (e.g. gradual, linear, hyperbolic), actions if withdrawal symptoms emerge, actions if deterioration or relapse occurs, mention of risk of confounding withdrawal symptoms with relapse, benefits and harms associated with tapering and discontinuing antidepressants, mention of any psychological challenges to discontinuing antidepressant treatment and mention of peer-support as a potential supportive measure. Text excerpts pertaining to tapering and discontinuing antidepressants were also extracted.

### Quality assessment

Two researchers (A.S. and K.M.) independently assessed the quality of the guidelines containing guidance on tapering or discontinuing antidepressants using the AGREE II tool,[21] covering 23 items in the domains of scope and purpose, stakeholder involvement, rigour of development, clarity of presentation, applicability and editorial independence. Items 9, 11, 12 and 15–21 were assessed specifically in relation to recommendations on tapering and discontinuation, whereas the remaining items were assessed by considering the guideline in total. The quality appraisal was therefore not an appraisal of the guidelines in their totality but specific for issues pertaining to tapering and discontinuing antidepressants. Guidelines not containing guidance on tapering or discontinuing were noted as 'not covered', and their quality was not assessed. Each item was scored on a 7-point Likert-type scale from 1 (*strongly disagree*) to 7 (*strongly agree*). A final quality score for each domain was reached by summing the scores for each item obtained by the two independent researchers and scaling the total as a percentage of the maximum possible score for each domain (percentage = obtained score − minimum score / maximum possible score − minimum possible score × 100). 'High quality' of a CPG was defined according to suggestions in the AGREE II user's manual as >70% on all domain scores. We then calculated the mean (*SD*) domain scores of each guideline. Finally, both researchers made an overall assessment for each CPG.

### Data synthesis and analysis

We constructed a recommendation matrix with all recommendations pertaining to tapering and discontinuing antidepressants and calculated the proportion of guidelines covering the different types of guidance. We presented the AGREE II scores for individual domains and in total and calculated the mean (*SD*) of each domain across the included guidelines. Based on individual domain scores, we identified issues that contributed substantially to decreasing the quality of the guidelines.

## Results

Our literature searches identified a total of 1123 hits (PubMed $n = 843$, guideline registries $n = 254$, manual website search $n = 26$). After removing duplicates, 868 unique records remained. After reviewing the titles and abstracts, we discarded 804 records. We examined the full text of the remaining 64 records and excluded a total of 38 records because they were either authored by an ineligible organisation ($n = 8$), not a CPG ($n = 10$), a later version of the CPG existed ($n = 15$), the CPG focused on a comorbid diagnosis ($n = 4$) and because the record pertained to a CPG that was no longer considered guidance for current practice by the organisation responsible for the CPG ($n = 1$). See Supplementary Table 2 for references to excluded records with reasons. In total, we included 21 unique CPGs (reported in 26 reco rds).[1–3,25–47] For one CPG,[31] we manually identified a newer version[48] not identified in any of our searches, which we included instead. The study selection process is illustrated in Figure 1.

### Guideline characteristics

Of the 21 CPGs, seven were from the United Sta tes,[26–30,32,48] five from the United Kingdom,[1,2,33,35,36] and one from Canada,[37] New Zealand,[39] Scotland,[40] Singapore,[41] Ireland[42] and Australia/New Zealand,[3] respectively. Three CPGs were issued by international organisations.[44,45,47] The CPGs were published between 1998 and 2020 (Table 2). Conflicts of interest for all authors were reported in 9 (43%) of the CPGs,[3,28–30,33,35–37,47] and at least one author reported a financial conflict of interest in all the 14 CPGs that reported financial conflicts of interest.[2,3,26,28,30,31,33,36,37,43]

### Guidance on tapering and discontinuation

The prevalence of the different types of guidance for tapering and discontinuation is illustrated in Figure 2, summarised in Tables 3 and 4, and described below. The text excerpts pertaining to the guidance are presented in Supplementary Table 3.

### Guidance on duration of tapering period and specific tapering regimen

Discontinuing antidepressants by gradually tapering the dose was recommended in 15 (71%) of the CPGs. Nine (43%) of the CPGs recommended a certain period of time to taper[1,2,36,39,41,44,45,47] ranging from at least 4 weeks[1,2,39,41,47] to 6 months (Table 4),[44] six (29%) of the CPGs did not specify the duration of taper, but recommended that antidepressants be 'tapered/discontinued slowly over an extended period of time',[3,26,27,48] or to 'taper over at least several weeks',[28,37] and the remaining six of the CPGs provided no guidance related to tapering. Rapid or abrupt discontinuation was

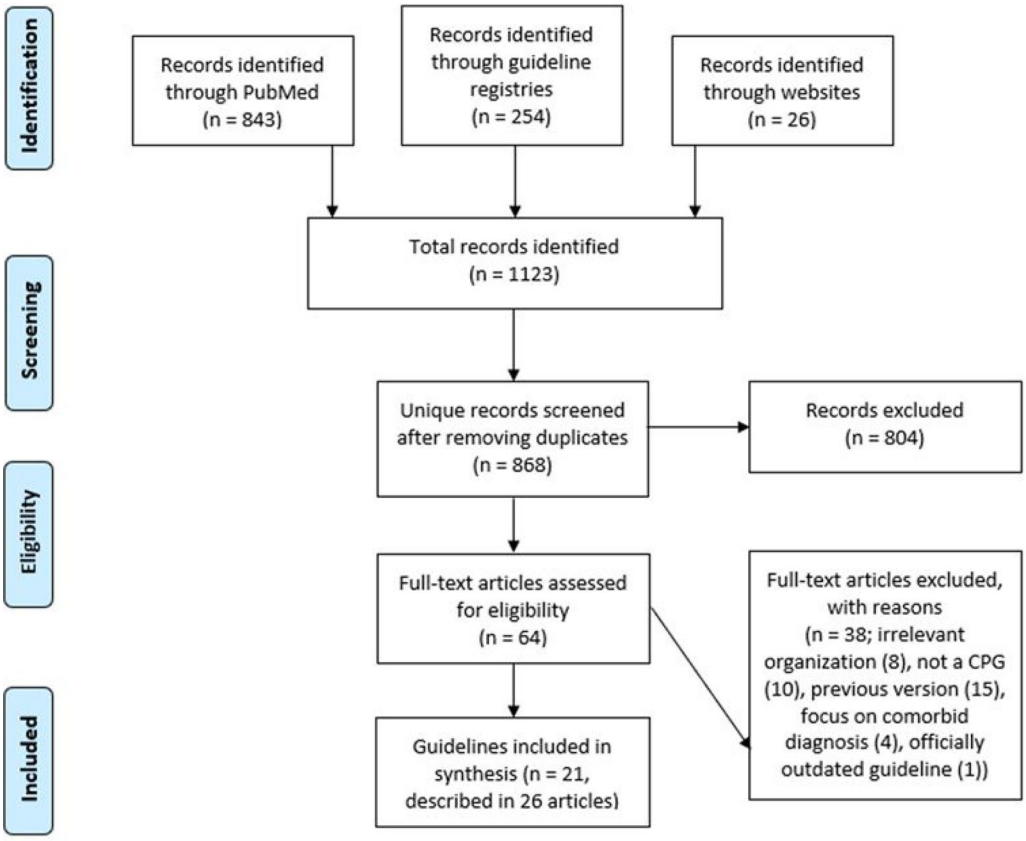


**Figure 1.** Flowchart of study selection process.

suggested in two (10%) of the CPGs, either when serious adverse events occurred[2] or for patients experiencing discontinuation symptoms despite a slow taper.[36] Specific guidance for short half-life drugs was provided in four (19%) CPGs, recommending 'a longer' taper;[1,28,36,41] and one stated that 'tapering should be guided by the elimination half-life of the medication', but without providing concrete guidance.[27] Specific guidance for tapering monoamine oxidase inhibitors was provided in one (5%) of the CPGs, recommending 'tapering over a longer period',[36] and for tapering tricyclic antidepressants in one (5%) of the CPGs, recommending 'a slow taper over a longer period of time'.[3]

Only two (10%) of the CPGs alluded to some form of guidance based on a specific dose-reduction regimen. Thus, one (5%) of the CPGs recommended halving the dose before discontinuation,[41] and one (5%) of the CPGs suggested that patients in high risk of severe discontinuation symptoms reduce the dose first to the minimal effective dose, then halve that dose, and then 'reduce more slowly in small decrements, allowing 2weeks for each dose reduction, according to how the tablet can be divided. [...] once minimum effective dose is achieved, reduce the dose by no more than 50% weekly'.[3]

### *Guidance on when to consider discontinuing antidepressant drug treatment*

Maintenance antidepressant treatment after symptomatic remission was recommended in 17 (81%) of the CPGs,[1–3,26–28,33,35–37,39,41,42,44,45,47,48] the majority recommending a period of 6 months,[1–3,26,27,33,36,37,39,41,42,44,45,48] although some CPGs recommended longer periods depending on the clinical situation and course of the illness. Only two (10%) of the CPGs, however, explicitly recommended that patients should discontinue their antidepressant after maintenance treatment[3] or continuation treatment;[28] the remaining CPGs provided no direct guidance on what to do when maintenance treatment ends. Other potential reasons for considering discontinuing antidepressants were pregnancy in three (14%) of the CPGs,[39–41] if symptoms of mania develop in one CPG (5%),[47] and if side effects develop early during treatment in two (10%) of the CPGs.[1,36]

**Table 2.** Characteristics of included guidelines.

| Source | Title | Country | Year | Issuing organisation |
|---|---|---|---|---|
| Agency for Health Care Policy and Research Practice Guidelines (AHCPR) | Treating major depression in primary care practice – an update of the Agency for Health Care Policy and Research Practice Guidelines[32] | US | 1998 | National health service |
| American Academy of Child and Adolescent Psychiatry (AACAP) | Practice parameter for the assessment and treatment of children and adolescents with depressive disorders[48] | US | 2007 | Professional society |
| American Academy of Pediatrics (AAP) | Guidelines for adolescent depression in primary care (GLAD-PC)): Part I. Practice preparation, identification, assessment and initial management + Part II. Treatment and ongoing management[26] | US | 2018 | Patient organisation + commercial company |
| American Psychological Association (APA) | Clinical practice guideline for the treatment of depression across three cohorts[29] | US | 2019 | Professional society |
| American Psychiatric Association (APA) | Practice guideline for the treatment of patients with major depressive disorder Third Edition[28] | US | 2010 | Professional society |
| American College of Physicians (ACP) | Nonpharmacologic *versus* pharmacologic treatment of adult patients with major depressive disorder: A clinical practice guideline from the American College of Physicians[30] | US | 2016 | Professional society |
| British Association for Psychopharmacology (BAP) | Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology guidelines[2] | UK | 2015 | Professional society |
| National Collaborating Centre for Mental Health (NCCMH) | Depression: The NICE guideline on the treatment and management of depression in adults – updated edition[36] | UK | 2019 | Professional society |
| Canadian Network for Mood and Anxiety Treatments (CANMAT) | Canadian network for mood and anxiety treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: Section 3. Pharmacological Treatments[37] | Ca | 2016 | Professional organisation |
| Department of Veteran Affairs and Department of Defense (VA/DoD) and The Management of Major Depressive Disorder Working Group | VA/DoD Clinical practice guideline for the management of major depressive disorder[27] | US | 2016 | Government |
| Health Service Executive (HSE) and Irish College of General Practitioners (ICGP) | Guidelines for the management of depression and anxiety disorders in primary care[42] | Ir | 2006 | Professional society |

*(Continued)*

**Table 2.** (Continued)

| Source | Title | Country | Year | Issuing organisation |
|---|---|---|---|---|
| Ministry of Health Singapore | Depression[41] | Si | 2012 | National health authority |
| National Institute for Health and Care Excellence (NICE) | Depression in adults – recognition and management[1] | UK | 2009 | Government |
| New Zealand Guidelines Group (NZGG) and Ministry of Health New Zealand | Identification of common mental disorders and management of depression in primary care[39] | NZ | 2008 | Government |
| National Institute for Health and Care Excellence (NICE) | Depression in children and young people – identification and management[33] | UK | 2019 | Government |
| Royal Australian and New Zealand College of Psychiatrists (RANZCP) | The 2020 Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders[3] | Aus, NZ | 2020 | Professional society |
| Royal College of Psychiatrists (RCPSYCH) and the Faculty of Old Age Psychiatry Working Group | Guideline for the management of late-life depression in primary care[35] | UK | 2003 | Professional society |
| Scottish Intercollegiate Guidelines Network (SIGN) and Healthcare Improvement Scotland (HSE) | Management of perinatal mood disorders[40] | Sc | 2012 | Government |
| World Federation of Societies of Biological Psychiatry (WFSBP) | World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for biological treatment of unipolar depressive disorders, Part 1: Update 2013 on the acute and continuation treatment of unipolar depressive disorders + Part 2: Maintenance treatment of major depressive disorder – update 2015[44] | Int | 2013 + 2015 | Professional organisation |
| World Federation of Societies of Biological Psychiatry (WFSBP) | Guidelines for biological treatment of unipolar depressive disorders in primary care[45] | Int | 2007 | Professional society |
| World Health Organization (WHO) | Mental Health Gap Action Programme (mhGAP) Intervention Guide for mental, neurological and substance use disorders in non-specialized health settings (2016) + WHO mhGAP Guideline Update (2015)[47] | Int | 2015 + 2016 | NGO |

Aus, Australia; Ca, Canada; Int, international; Ir, Ireland; mhGAP, Mental Health Gap Action Programme; NGO, non-governmental organisation; NZ, New Zealand; UK, the United Kingdom; US, the United States of America; Sc, Scotland; Si, Singapore.

### *Guidance on actions if withdrawal symptoms emerge*

Some form of guidance on how to manage withdrawal symptoms was mentioned in five (24%) of the CPGs.[1,2,28,36,39] These recommendations included single statements on providing an explanation and reassurance ($n=4$, 19%),[1,2,28,36] monitoring symptoms ($n=2$, 10%),[1,36] resuming the

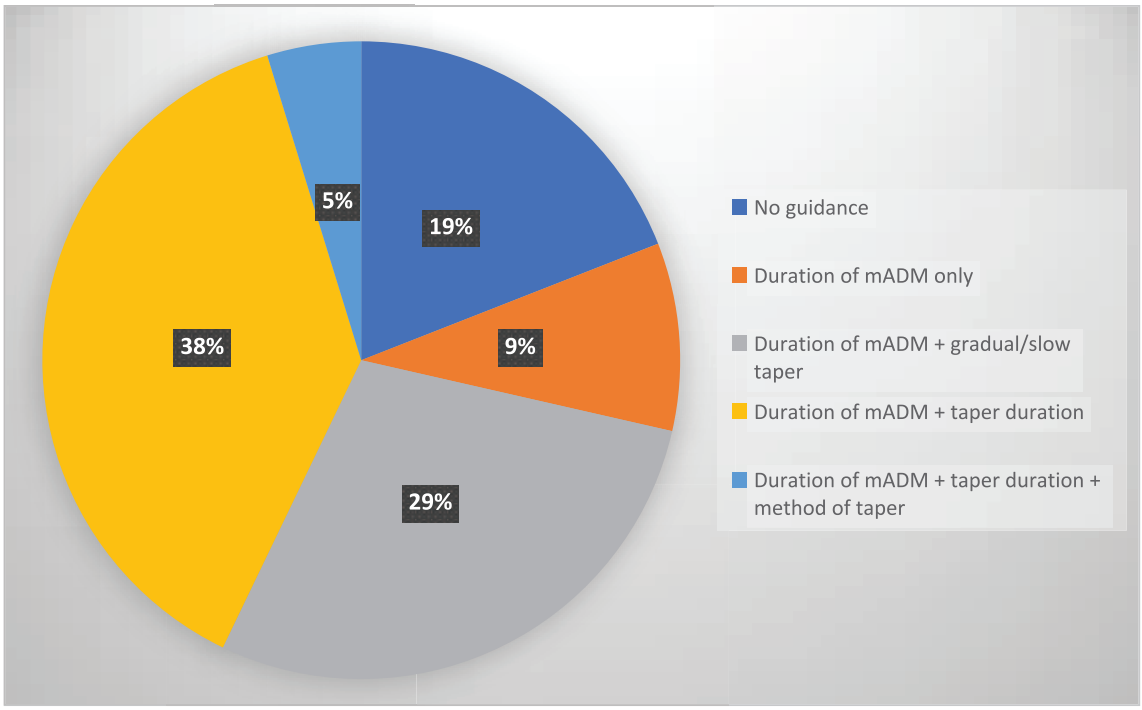


**Figure 2.** Prevalence of guidance on tapering in clinical practice guidelines on depression.
mADM, maintenance antidepressant medication.

antidepressant and tapering more slowly ($n=4$, 19%),[1,2,36,39] tapering more gradually ($n=1$, 5%),[28] switching to fluoxetine and stopping after withdrawal symptoms have resolved ($n=2$, 10%),[2,28] and switching to a similar drug with longer half-life and then taper more gradually while monitoring symptoms ($n=2$, 10%).[1,36] No other details or elaboration were provided.

Two (10%) other CPGs stated that withdrawal symptoms and relapse should be differentiated from each other when discontinuing antidepressants, but without considering the potential overlap of symptoms between these situations.[3,44]

Potential benefits of coming off antidepressant were not mentioned in any CPG.

### *Mention of potential benefits and harms associated with tapering and discontinuing antidepressants*

The potential for withdrawal symptoms to emerge upon discontinuing or reducing antidepressants was mentioned in 15 of the (71%) CPGs,[1–3,26–28,33,36,37,39,41,42,44,45,48] and depressive relapse/recurrence was mentioned as a potential harm in 14 (67%) CPGs.[1–3,26–28,36,39–41,44,45,47,48] In 12 (57%) CPGs, both withdrawal symptoms and relapse/recurrence were mentioned as potential harms (Table 3), and of these, 4 (19%) included a specific statement on the risk of misinterpreting withdrawal symptoms as depressive relapse, stating that withdrawal symptoms may 'mimic',[48] 'be misdiagnosed as',[2] 'mistaken for'[28] or 'be hard to distinguish from'[36] relapse of depressive symptoms.

### *Psychological challenges and supportive measures when tapering and discontinuing antidepressants*

None of the CPGs mentioned or provided guidance on any psychological challenges to discontinuing antidepressants or mentioned psychological or peer-support measures to support patients coming off antidepressants.

### *Patients' views and preferences on tapering and discontinuing antidepressants*

None of the CPGs stated having sought patients' views and preferences on issues related to tapering and discontinuing antidepressants. Qualitative studies on patients' experiences were similarly not included in any of the CPGs.

**Table 3.** Guidance on tapering and discontinuing antidepressants mentioned in clinical practice guidelines on depression.

| | mADM duration | Gradual tapering | Hyperbolic tapering | Duration of taper | Dose-reduction regimen | WS actions | Relapse actions | WS as harm | Relapse as harm | Symptomatic overlap | Benefits mentioned | Psychological barriers | Peer-support |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *N* (%) | 17 (81%) | 15 (71%) | 0 (0%) | 9 (43%) | 2 (10%) | 5 (24%) | 4 (19%) | 15 (71%) | 14 (67%) | 4 (19%) | 0 (0%) | 0 (0%) | 0 (0%) |
| American Psychiatric Association[28] | + | + | – | – | – | + | + | + | + | + | – | – | – |
| BAP[2] | + | + | – | + | – | + | + | + | + | + | – | – | – |
| NCCMH[36] | + | + | – | + | – | + | – | + | + | + | – | – | – |
| NICE[1] | + | + | – | + | – | + | – | + | + | – | – | – | – |
| NZGG[39] | + | + | – | + | – | + | – | + | + | – | – | – | – |
| NICE[33] | + | + | – | + | – | – | – | + | – | – | – | – | – |
| WFSBP[44] | + | + | – | + | – | – | + | + | + | – | – | – | – |
| WFSBP[45] | + | + | – | + | – | – | + | + | + | – | – | – | – |
| WHO[47] | + | + | – | + | – | – | – | – | + | – | – | – | – |
| CANMAT[37] | + | + | – | – | – | – | – | + | – | – | – | – | – |
| AAP[26] | + | + | – | – | – | – | – | + | + | – | – | – | – |
| VA/DoD[27] | + | + | – | – | – | – | – | + | + | – | – | – | – |
| AACAP[48] | + | + | – | – | – | – | – | + | + | + | – | – | – |
| RANZCP[3] | + | + | – | – | + | – | – | + | + | – | – | – | – |
| MoH (Si)[41] | + | + | – | + | + | – | – | + | + | – | – | – | – |
| HSE[42] | + | – | – | – | – | – | – | + | – | – | – | – | – |
| SIGN[40] | – | – | – | – | – | – | – | – | + | – | – | – | – |
| RCPSYCH[35] | + | – | – | – | – | – | – | – | – | – | – | – | – |
| AHCPR[32] | – | – | – | – | – | – | – | – | – | – | – | – | – |
| APA[29] | – | – | – | – | – | – | – | – | – | – | – | – | – |
| ACP[30] | – | – | – | – | – | – | – | – | – | – | – | – | – |

AACAP, American Academy of Child and Adolescent Psychiatry; AAP, American Academy of Pediatrics; ACP, American College of Physicians; AHCPR, Agency for Health Care Policy and Research Practice Guidelines; APA, American Psychological Association; BAP, British Association for Psychopharmacology; CANMAT, Canadian Network for Mood and Anxiety Treatments; HSE, Health Service Executive; mADM, maintenance antidepressant medication; MoH (Si), Ministry of Health, Singapore; NCCMH, National Collaborating Centre for Mental Health; NICE, National Institute for Health and Care Excellence; NZGG, New Zealand Guidelines Group; RANZCP, Royal Australian and New Zealand College of Psychiatrists; RCPSYCH, Royal College of Psychiatrists; Relapse actions, guidance on actions if relapse or deterioration in general occurs; Relapse as harm, mention of relapse as a possible harm of tapering or discontinuing antidepressants; SIGN, Scottish Intercollegiate Guidelines Network; Symptomatic overlap, mention of the symptomatic overlap between withdrawal symptoms and relapse; VA/DoD, Department of Veteran Affairs and Department of Defense; WFSBP, World Federation of Societies of Biological Psychiatry; WHO, World Health Organization; WS, withdrawal symptoms; WS actions, guidance on actions if withdrawal symptoms occur; WS as harm, mention of withdrawal symptoms as a possible harm of tapering or discontinuing antidepressants. '+' indicates that the item was mentioned in the guideline. '–' indicates that the item was not mentioned in the guideline.

**Table 4.** Summary of recommendations on discontinuation and tapering of antidepressants in clinical practice guidelines on depression.

| Source and year | Duration of mADM | Duration of taper | Actions if discontinuation symptoms emerge | Actions if deterioration/ relapse occurs |
|---|---|---|---|---|
| BAP[2] | 6 mo–>2 yr | >4 wks–some months | Explanation and reassurance; resume AD and taper more slowly; switch to fluoxetine and stop | Restart an AD; reestablish previous dose |
| RANZCP[3] | >6 mo | Slowly | – | – |
| HSE + ICGP[42] | >6 mo–12 mo | – | – | – |
| CANMAT[37] | 6 mo–>2 yr | Several weeks | – | – |
| WFSBP[44] | >6 mo–lifetime | >3 mo to 4–6 mo | – | Resume full dose for at least 6 months |
| AAP[26] | 6 mo–1 year | Slow taper | | – |
| SIGN + HIS[40] | – | – | – | – |
| VA/DoD[27] | >6 mo–indefinitely | Slow taper | – | – |
| WHO[46,47] | >9–12 mo | >4 wk | – | – |
| American Psychiatric Association[28] | 4 mo–indefinitely | Several weeks–a longer period | Reassurance and a more gradual taper; switch to fluoxetine and stop | Resume AD treatment; monitor symptoms |
| APA[29] | – | – | – | – |
| ACP[30] | – | – | – | – |
| NZGG + MoH (NZ)[39] | >6 mo–>2 yr | 4 wk | Resume AD and taper more slowly | – |
| NICE[33] | >6 mo | 6–12 wk | | – |
| WFSBP[45] | >6 mo–lifetime | >6 wk to 4–6 mo | – | Resume full dose for at least 6 months |
| AACAP[48] | >6 mo–indefinitely | Slowly | – | – |
| NICE[1] | >6 mo–>2 yr | 4 wk–longer | Seek advice from practitioner; monitoring and reassurance; resume AD and taper more gradually; start another AD with longer half-life and taper more gradually | – |
| AHCPR[32] | – | – | – | – |
| RCPSYCH[35] | >1–> 3 yr | – | – | – |
| MoH (SI)[41] | 6 mo–lifelong | Abrupt[a] >4 wk | – | – |
| NCCMH[36] | >6 mo–>2 yr | Abrupt[b] –4 wk–longer | Seek advice from practitioner; monitoring and reassurance; resume AD and taper more gradually; start another AD with longer half-life and taper more gradually; counsel patients; abrupt withdrawal | – |

AACAP, American Academy of Child and Adolescent Psychiatry; AAP, American Academy of Pediatrics; ACP, American College of Physicians; AD, antidepressant; AHCPR, Agency for Health Care Policy and Research Practice Guidelines; APA, American Psychological Association; BAP, British Association for Psychopharmacology; CANMAT, Canadian Network for Mood and Anxiety Treatments; HIS, Healthcare Improvement Scotland; HSE, Health Service Executive; ICGP, College of General Practitioners; mADM, maintenance antidepressant medication; mo, months; MoH (Si), Ministry of Health, Singapore; NCCMH, National Collaborating Centre for Mental Health; NICE, National Institute for Health and Care Excellence; NZ, New Zealand; NZGG, New Zealand Guidelines Group; RANZCP, Royal Australian and New Zealand College of Psychiatrists; RCPSYCH, Royal College of Psychiatrists; SIGN, Scottish Intercollegiate Guidelines Network; VA/DoD, Department of Veteran Affairs and Department of Defense; WFSBP, World Federation of Societies of Biological Psychiatry; WHO, World Health Organization; wk, weeks; yr, years.
[a]'Fluoxetine dose of 20 mg can be abruptly stopped and doses of above 20 mg recommended to reduce over a period of 2 weeks'.
[b]'This is not required with fluoxetine because of its long half-life'.

### *AGREE II quality assessment*

Outcomes of our AGREE 2 appraisal are presented in Table 5. CPG quality was generally rated as low and varied considerably between CPGs and within the domains. The overall rating of the guidance on tapering and discontinuing antidepressants ranged between 8% and 33% (mean 17%, *SD* 8%). No CPG reached the predefined score of >70% in all domains indicating 'high quality'. Details on the assessment of each domain are provided in Supplementary Table 4.

## Discussion

For this first systematic review of guidance on tapering and discontinuing antidepressants in CPGs on depression, we included 21 CPGs issued by national health authorities and major national or international professional organisations or societies in English-speaking high-income countries.

We found that most CPGs recommended that antidepressants are tapered slowly or gradually when discontinued but that very few CPGs specified what was understood by gradual or slow tapering or provided any concrete guidance on a specific dose-reduction regimen. None of the CPGs included the antidepressant discontinuation phase in their treatment algorithms or flow charts, and guidance or considerations on when to discontinue antidepressant treatment was generally scarce with very few CPGs explicitly recommending discontinuing antidepressants after maintenance or continuation treatment. Although most CPGs mentioned that withdrawal symptoms can occur, they rarely considered how to address potential withdrawal symptoms and help patients manage them, and potential psychological challenges were not addressed in any CPG. The quality of the CPGs, as assessed using the AGREE II tool, was overall low and none reached our predefined threshold for 'high-quality'.

### *Implications*

Our findings have several clinical implications. First, the limited and vague guidance on tapering and discontinuation in current CPGs, which was hard to find in many cases, means that they provide little support for clinicians seeking to help patients stop or taper antidepressants. This may have the consequence that clinicians are hesitant to support patients in a process of discontinuing antidepressants. Second, the recommendation in the majority of the CPGs to taper over a given period of time, without considering the specific dosing regimen, implied that the tapering suggested was a linear one and that a proper taper was defined as a slow taper in terms of overall duration. This may be problematic as taper duration is subordinate if the dose reductions involve a high risk of causing withdrawal symptoms. This has been suggested to be the case for antidepressants when tapering using standard available doses, especially for the last reductions before cessation due to the large biological effects even at very low and subtherapeutic doses.[12,16,49] Withdrawal symptoms have thus been reported even after very small dose reductions, especially in the lower dose range,[12] which would not be mitigated by even the slowest taper, as what is needed is smaller dose reductions, not longer time. The hyperbolic relationship between antidepressant dose and occupancy of their primary target receptor, the serotonin transporter,[49] suggests that the gradual reduction in the biological effect likely necessary to mitigate withdrawal symptoms requires a hyperbolic dose-reduction regimen.[12] This requires performing multiple dose reductions even below half of the lowest standard manufactured doses, which is practically impossible using standard available doses, as the pills are simply too potent at very low doses and cannot be evenly split into small enough units. Such a regimen was not recommended by any CPG. Third, the symptomatic overlap between potential withdrawal symptoms and depressive symptoms was acknowledged in only very few CPGs, and guidance on how to discern between these two fundamentally different clinical situations was not provided. Lack of such guidance may have the consequence that drug treatment is continued unnecessarily in some patients if withdrawal reactions are misdiagnosed as relapse, potentially leading to resuming drug treatment under the false assumption that the antidepressant was necessary to prevent relapse. Better and more concrete guidance could potentially help distinguish clinically between patients who deteriorate due to withdrawal from those with genuine relapse. Finally, the lack of guidance on supporting patients manage withdrawal symptoms, including psychological- and peer-support measures, may lead some patients experiencing such symptoms to stop ongoing efforts to discontinue antidepressants. Recommendations in CPGs on various supportive measures and their implementation could provide valuable help for clinicians aiming to support patients discontinuing or tapering antidepressants

**Table 5.** Quality appraisal of guidance on stopping and tapering antidepressants in clinical practice guidelines on depression using the AGREE II tool.

| Guideline | AGREE II domain scores (%) | | | | | | |
|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | Overall |
| BAP[2] | 58 | 44 | 14 | 28 | 0 | 38 | 17 |
| RANZCP[3] | 39 | 39 | 18 | 39 | 0 | 42 | 25 |
| HSE + ICGP[42] | 31 | 25 | 0 | 8 | 0 | 0 | 8 |
| CANMAT[37] | 50 | 28 | 25 | 19 | 6 | 50 | 8 |
| WFSBP[44] | 64 | 22 | 19 | 31 | 0 | 25 | 17 |
| AAP[26] | 78 | 44 | 18 | 0 | 0 | 13 | 8 |
| SIGN + HIS[40] | 75 | 50 | 27 | 22 | 0 | 4 | 8 |
| VA/DoD[27] | 78 | 61 | 50 | 17 | 8 | 8 | 17 |
| WHO[46,47] | 94 | 69 | 43 | 11 | 27 | 58 | 17 |
| American Psychiatric Association[28] | 42 | 11 | 27 | 19 | 0 | 38 | 25 |
| NZGG + MoH (NZ)[29] | 78 | 47 | 24 | 25 | 17 | 71 | 25 |
| NICE[33] | 92 | 78 | 41 | 17 | 13 | 42 | 25 |
| WFSBP[45] | 58 | 19 | 22 | 19 | 4 | 25 | 17 |
| AACAP[48] | 53 | 14 | 27 | 19 | 0 | 13 | 17 |
| NICE[1] | 83 | 83 | 43 | 33 | 21 | 54 | 33 |
| RCPSYCH[35] | 33 | 3 | 30 | 14 | 0 | 17 | 8 |
| MoH (SI)[41] | 50 | 56 | 18 | 25 | 4 | 0 | 8 |
| NCCMH[36] | 56 | 58 | 36 | 33 | 8 | 50 | 25 |
| Mean (*SD*) | 62 (20) | 42 (23) | 27 (12) | 21 (10) | 6 (8) | 30 (22) | 17 (8) |

AACAP, American Academy of Child and Adolescent Psychiatry; AAP, American Academy of Pediatrics; APA, American Psychological Association; BAP, British Association for Psychopharmacology; CANMAT, Canadian Network for Mood and Anxiety Treatments; HIS, Healthcare Improvement Scotland; HSE, Health Service Executive; ICGP, College of General Practitioners; MoH (Si), Ministry of Health, Singapore; NCCMH, National Collaborating Centre for Mental Health; NICE, National Institute for Health and Care Excellence; NZ, New Zealand; NZGG, New Zealand Guidelines Group; RANZCP, Royal Australian and New Zealand College of Psychiatrists; RCPSYCH, Royal College of Psychiatrists; SD, Standard deviation; SIGN, Scottish Intercollegiate Guidelines Network; VA/DoD, Department of Veteran Affairs and Department of Defense; WFSBP, World Federation of Societies of Biological Psychiatry; WHO, World Health Organization. Values represent the mean of the scores of individual researchers. Domain 1: scope and purpose; domain 2: stakeholder involvement; domain 3: rigour of development; domain 4: clarity of presentation; domain 5: applicability; domain 6: editorial independence.

just as guidance on helping patients minimise potential psychological dependency of antidepressants treatment would be helpful.

Our findings also have implications for research and the possibility to provide evidence-based guidance for clinicians. First, the limited clinical evidence-base for any tapering or discontinuation regimen poses a challenge for guideline developers wishing to provide concrete, evidence-based recommendations. Thus, randomised clinical trials (RCTs) investigating interventions for tapering and discontinuing antidepressants are few and have important methodological limitations, and the

certainty of the evidence is, taken together, very low.[20] These limitations in the supporting evidence-base were largely unacknowledged in the CPGs, however. In the absence of RCTs, tapering guidance could be informed by other types of evidence such as non-randomised and retrospective studies of tapering strips,[17,18] pharmacologically rational theory on withdrawal symptoms and dose-reduction regimens,[12,49] patients' experiences of undergoing withdrawal,[50] and expert knowledge,[51] which could be synthesised for that purpose. Until RCT data become available, such lines of evidence could potentially support recommendations to clinicians on how to help patients taper antidepressants; importantly, while emphasising the inherent limitations of such types of evidence. Generally, an approach to tapering of trial and error with shared decision-making, acknowledging the many uncertainties of antidepressant tapering and withdrawal symptoms, may be recommended at this stage. Second, the low quality of the guidelines as assessed using AGREE II point to a need for future CPGs to improve in several areas, especially those concerning the rigour of development and the clarity of presentation, including clearly linking supporting evidence with recommendations and to make clear when recommendations are based on low certainty evidence and to make recommendations on tapering and discontinuation clear and readily accessible.

### *Limitations*

Our study has several review-level limitations. First, we only included CPGs published in English and may thus have missed CPGs that impact clinical practice in non-English-speaking countries, where we encourage a similar systematic review to be conducted. However, given our inclusion criteria, we believe we are likely to have included those CPGs that internationally have the most impact on clinical practice. Second, there are no validated threshold in the AGREE II tool to distinguish between high- and low-quality CPGs and the cutoff we used, while suggested in the AGREE II guidance, may by some be considered too conservative. Third, the categorisation of recommendations and the quality appraisal using AGREE II involves subjective judgements, and it is possible that others would have interpreted the data differently than we did. We adhered to prespecified methods outlined in our protocol with two independent researchers doing duplicate data extraction and quality appraisal and feel confident that most readers would arrive at the same conclusions we did; our judgements and other extracted data, including supporting statements pertaining to guidance on stopping or tapering in the CPGs and AGREE II assessment forms, are provided as Supplementary Tables.

## Conclusion

Current major CPGs provide only scarce and vague guidance to clinicians on how to help patients taper and discontinue antidepressants safely. The guidance provided, which often implied the use of linear tapering of antidepressants, could potentially increase the risk of withdrawal symptoms, and the lack of guidance on the practical distinction between withdrawal and relapse could lead to unnecessary long-term treatment in some patients. Better guidance requires better randomised trials investigating interventions for discontinuing or tapering antidepressants.

## Author contributions

**Anders Sørensen:** Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Validation; Visualization; Writing – original draft; Writing – review & editing

**Karsten Juhl Jørgensen:** Conceptualization; Methodology; Supervision; Validation; Writing – review & editing

**Klaus Munkholm:** Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Supervision; Validation; Writing – review & editing.

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## Data availability

All data is available in the published article and the accompanying online supplemental material.

## Supplemental material

Supplemental material for this article is available online.

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**Supplementary Table 1.** List of guideline registries, databases, and websites searched.

| Database | Link | Search terms and filters | Total results | Full text |
|---|---|---|---|---|
| **Journal databases** (25 May 2021) | | | | |
| PubMed | www.ncbi.nlm.nih.gov/pubmed | (Depression[TI] OR "Depressive Disorder"[Mesh] OR "Depression"[Mesh]) AND (guideline[Publication Type] OR guideline*[TI]). | 843 | 94 |
| **Guideline registries** (25 May 2021) | | | | |
| National Institute for Health and Care Excellence - UK (NICE) | www.nice.org.uk/<br><br>https://www.nice.org.uk/guidance/conditions-and-diseases/mental-health-and-behavioural-conditions/depression/products?ProductType=Guidance&Status=Published | Depression<br>Filter: Guidance | 9 | 4 |
| Standards and Guidelines Evidence (SAGE) | https://www.partnershipagainstcancer.ca/news-events/news/article/sage-standards-and-guidelines-evidence/# | Depression | 0 | 0 |
| American College of Physicians Clinical Practice Guidelines | www.acponline.org/clinical-information/guidelines<br><br>https://www.acponline.org/clinical-information/guidelines | Depression | 1 | 1 |
| National Health and Medical Research Council (NHMRC): Clinical Practice Guidelines | https://www.nhmrc.gov.au/health-advice/guidelines | Depression | 0 | 0 |
| New Zealand Guidelines Group | www.health.govt.nz/about-ministry/ministry-health-websites/new-zealand-guidelines-group<br><br>https://www.health.govt.nz/publications/depression | Depression<br>Filter: Guides and Standards | 2 | 1 |
| eGuidelines | www.eguidelines.co.uk<br><br>*Forwards to:* https://www.mgp.co.uk/ | Depression | 0 | 0 |
| Guidelines.co.uk | https://www.guidelines.co.uk<br><br>https://www.guidelines.co.uk/searchresults?qkeyword=Depression&PageSize=10&parametrics=&cmd=AddPm&val=WVFACET1%7C20113&keywords=Depression | Depression | 5 | 4 |
| Guidelines International Network (G-I-N) library | www.g-i-n.net<br><br>https://guidelines.ebmportal.com/guidelines-international-network?search=depression&type=search | Depression | 37 | 5 |
| Scottish Intercollegate Guidelines Network (SIGN) | www.sign.ac.uk<br><br>https://www.sign.ac.uk/our-guidelines/ | *No search function. All guidelines were screened* | 160 | 1 |
| National Guideline Clearinghouse (NGC) | www.guidelines.gov<br><br>*Forwards to:* https://www.ahrq.gov/gam/index.html<br><br>https://www.ahrq.gov/prevention/guidelines/archive.html | Depression | 2 | 1 |
| Canadian Medical Association Infobase: Clinical Practice Guidelines (CPG) | www.cma.ca/En/Pages/clinical-practice-guidelines.aspx<br><br>https://joulecma.ca/cpg/homepage/?q=Depression | Depression | 22 | 3 |

| | | | | |
|---|---|---|---|---|
| National Library for Health Guidelines Finder (UK) | *Could not be found* | - | - | - |
| RNAO Best Practice Guidelines | www.rnao.ca/bpg<br><br>https://rnao.ca/bpg/bpg-search?type=All&field_project_initiative_nid=All&keys=depression | Depression | 14 | 2 |
| Magic | https://magicevidence.org/ | Depression | 2 | 0 |
| **Other** | | | | |
| Google | www.google.com | First 100 hits on "clinical practice guideline" or "guideline" + depression" | 100 | 0 |

| |
|---|
| **Websites** (25 May 2021) |
| https://www.gov.uk/government/organisations/department-of-health-and-social-care |
| https://www.gov.uk/government/organisations/public-health-england |
| https://www.nhs.uk/ |
| https://www.rcpsych.ac.uk/improving-care/nccmh |
| https://www.bps.org.uk/ |
| https://www.nice.org.uk/ |
| https://www.bap.org.uk/ |
| https://www.nimh.nih.gov/index.shtml |
| https://www.hhs.gov/ |
| https://health.gov/ |
| https://www.psychiatry.org/ |
| https://www.apa.org |
| https://www.ashp.org/?loginreturnUrl=SSOCheckOnly |
| https://www.americangeriatrics.org |
| https://www.aagponline.org/ |
| https://www.acpm.org/ |
| https://www.acponline.org/ |
| https://www.aap.org/en-us/Pages/Default.aspx |
| https://www.uspreventiveservicestaskforce.org/uspstf/ |
| https://www.healthquality.va.gov/guidelines/MH/mdd/ |
| https://adaa.org/living-with-anxiety/ask-and-learn/resources# |
| https://www.canada.ca/en/health-canada.html |
| https://www.canada.ca/en/public-health.html |
| https://cihr-irsc.gc.ca/e/193.html |
| https://www.cpa-apc.org/ |
| https://cpa.ca/ |
| https://www.cadth.ca/ |
| https://www.canmat.org/ |
| https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/msp/committees/guidelines-and-protocols-advisory-committee-gpac |
| https://www.hqontario.ca/ |
| https://mdsc.ca/ |
| https://cmha.ca/ |
| https://www.nhmrc.gov.au/ |
| https://www.beyondblue.org.au/health-professionals/clinical-practice-guidelines?fbclid=IwAR0HgDPfOeVUKZmcIdHrSFykCHgps1c58wI-M9yOYzRRXXKY1vfl5NNlHlY |
| https://www.health.gov.au/ |
| https://www.ranzcp.org/home |
| https://www.psychology.org.au/ |
| https://www.anzappl.org/ |
| https://anzmh.asn.au/ |
| https://napp.org.au/ |
| https://orygen.org.au/ |
| https://www.gov.ie/en/organisation/department-of-health/ |
| https://publichealth.ie/ |
| https://www.hse.ie/eng/ |
| https://www.irishpsychiatry.ie/ |
| https://www.psychologicalsociety.ie/ |
| https://www.mentalhealthireland.ie/ |
| www.icgp.ie |

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|---|
| https://www.health.govt.nz/ |
| https://www.health.govt.nz/about-ministry/ministry-health-websites/new-zealand-guidelines-group |
| https://www.irishpsychiatry.ie/ |
| https://www.psychology.org.nz/ |
| http://www.psychologistsboard.org.nz/ |
| https://www.moh.gov.sg/hpp/all-healthcare-professionals/guidelines |
| https://www.singaporepsychiatry.org.sg/ |
| https://singaporepsychologicalsociety.org/ |
| https://www.wfsbp.org/home/ |
| https://www.who.int/ |
| https://www.europsy.net/ |
| https://www.wpanet.org/ |
| https://wfmh.global/ |
| http://www.isapp.org/ |
| https://iacapap.org/ |
| https://sobp.org/ |
| https://www.cinp.org |

**Supplementary Table 2.** List of excluded studies with reasons.

**Later version of the CPG existed (15)**


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## Not a CPG (N=10)


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### The guideline focused on a comorbid diagnosis (4)

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## CPG that was no longer considered guidance for current practice by the organization responsible for the guideline (1)

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**Supplementary Table 3.** Full quotes pertaining to guidance or information on stopping or tapering antidepressants.

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| **When to consider stopping antidepressants** | |
| **SIGN + HIS 2012**[1] | If a woman taking psychotropic drugs is planning a pregnancy, consideration should be given to discontinuing treatment if the woman is well and at low risk of relapse.<br><br>General practitioners should review antidepressant therapy as soon as possible in pregnancy to discuss whether the current medication should be continued and any other alternative pharmacological or non-pharmacological treatments initiated. |
| **NZGG + MoH 2008**[4] | If a woman who is pregnant or planning pregnancy is being treated with an antidepressant, her treatment preference, previous history and risk should be reviewed. If appropriate, attempts should be made to withdraw the antidepressant and substitute an alternative treatment and/ or ensure that the antidepressant with the lowest risk profile is used.<br><br>Unplanned conception for a woman on antidepressants may prompt her to abruptly stop taking the medication, incurring high risk of recurrence of depression before delivery. [475] Careful reassessment of risks will help women to decide whether continuation of antidepressants is appropriate. [453]<br><br>If a woman on antidepressants is planning conception, she may wish to attempt slow withdrawal from her medication before conception, provided the depression has receded. |
| **NICE 2009**[5] | If a person with depression develops side effects early in antidepressant treatment, provide appropriate information and consider one of the following strategies: 1) monitor symptoms closely where side effects are mild and acceptable to the person or 2) stop the antidepressant or change to a different antidepressant if the person prefers or 3) in discussion with the person, consider short-term concomitant treatment with a benzodiazepine if anxiety, agitation and/or insomnia are problematic (except in people with chronic symptoms of anxiety); this should usually be for no longer than 2 weeks in order to prevent the development of dependence. |
| **NCCMH 2010**[6] | If a person with depression develops side effects early in antidepressant treatment, provide appropriate information and consider one of the following strategies: monitor symptoms closely where side effects are mild and acceptable to the person or … stop the antidepressant or change to a different antidepressant if the person prefers or … in discussion with the person, consider short-term concomitant treatment with a benzodiazepine if anxiety, agitation and/or insomnia are problematic (except in people with chronic symptoms of anxiety); this should usually be for no longer than 2 weeks in order to prevent the development of dependence. |
| **WHO 2015-2016**[7] | If symptoms of mania develop, tell the person and the carers to stop the antidepressant immediately and return for help.<br><br>If the person develops a manic episode, stop the antidepressant immediately; it may trigger a manic episode in untreated bipolar disorder. |
| **APA 2010**[8] | If maintenance-phase treatment is not indicated, stable patients may be considered for discontinuation of treatment after the continuation phase.<br><br>The decision to discontinue treatment should be based on the same factors considered in the decision to initiate maintenance treatment (Table 10), including the probability of recurrence, the frequency and severity of past episodes, the persistence of depressive symptoms after recovery, the presence of co-occurring disorders, and patient preferences.<br><br>In terms of timing, patients should be advised not to discontinue medications before holidays, significant events (e.g., weddings), or stressful events. |
| **Duration of maintenance antidepressant treatment** | |
| **BAP 2015**[9] | Medication-responsive patients should have their medication continued at the acute treatment dose after remission with the duration determined by risk of relapse. In patients at lower risk of relapse (e.g. first-episode patients without other risk factors) the duration should be at least 6–9 months after full remission. Duration in other cases should be tailored to the individual relapse risk; consider a duration of at least 1 year after full remission in patients with any increased risk of relapse. In higher-risk patients (e.g. more than five lifetime episodes and/or two episodes in the last few years) at least 2 years should be advised and for most long-term treatment should be considered. |
| **RANZCP 2020**[10] | A minimum duration of 6 months remains a reasonable recommendation, supported by a recent meta analysis. |
| **HSE + ICGP 2006**[11] | Continue treatment (minimum 6-12 months) on recovery.<br><br>For patients with a depressive episode, continue antidepressants for at least 6 months following remission. Continuation of antidepressants beyond this will depend on the number of previous episodes, presence of residual symptoms, and concurrent psychosocial difficulties. |
| **CANMAT 2016**[12] | The 2009 guidelines recommended that patients maintain treatment with antidepressants for 6 to 9 months after achieving symptomatic remission, while those with risk factors for recurrence extend antidepressant treatment to 2 years or more. New evidence continues to support this recommendation for antidepressant maintenance. [82] |
| **WFSBP 2013 + 2015**[2] | The continuation phase of treatment lasts at least 6 months following remission of the acute symptomatology. Treatment should be prolonged to 9 months in patients with a history of long previous episodes, and should continue even longer in cases of residual symptomatology and until such symptoms have subsided and in psychotic depression. [clinical consensus]<br><br>Continuation of successful treatment for 6 – 9 months after remission of the acute depressive episode should be recommended. Even though no definite recommendation can be given as to when prophylactic therapy beyond these 6 – 9 |

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| | months is warranted, it is clearly indicated in situations associated with a high risk of recurrence or consequences. For patients who have had three or more episodes of major depression and in patients with a high prior rate of recurrence (e.g., two episodes within 5 years), longer-term maintenance therapy is indicated. Besides a high number of previous episodes adverse prognostic indicators for recurrence include, residual symptoms at remission, previous longer episodes and chronicity, more severe previous episodes, onset early in life, concurrent dysthymic disorder ("double depression"), relapse/recurrence after medication withdrawal, previous episode in the last year, concurrent substance abuse or anxiety disorders, and family history of MDD in first degree relatives.<br><br>The duration of continuation treatment following remission of the acute depressive episode should be 6 – 9 months. Treatment length required for maintenance treatment beyond that point is not yet fully determined. Duration may vary from 3 years to lifetime, but in general the more adverse the prognosis, the longer the maintenance therapy. Three years of maintenance therapy is most commonly appropriate for recurrent patients, particularly when an episode prior to the present one has occurred in the last 5 years or when remission has been difficult to achieve. Maintenance treatment for 5 – 10 years or even indefinitely is recommended for those patients at greater risk, particularly when two or three attempts to withdraw medication have been followed by another episode within a year.<br><br>Three years maintenance therapy is appropriate almost as a routine for recurrent patients, particularly where an episode prior to the present one has occurred in the last 5 years or where remission has been difficult to achieve. Maintenance for 5 years or indefinitely is recommended for those patients at greater risk, particularly where two or three attempts to withdraw medication have been followed by another episode within a year.<br><br>Three years of maintenance therapy is most commonly appropriate for recurrent patients, particularly when an episode prior to the present one has occurred in the last 5 years or when remission has been difficult to achieve. Maintenance treatment for 5 – 10 years or even indefinitely is recommended for those patients at greater risk, particularly when two or three attempts to withdraw medication have been followed by another episode within a year.<br><br>There is good evidence from a controlled 5-year study that patients who benefit the most from continued prophylaxis were those receiving active full-dose medication for at least 5 years. [Kupfer et al. 1992] Thus, for some patients, maintenance treatment is required for very long periods (e.g., a decade) and for others it is required indefinitely. [Lam 2009] |
| **AAP 2018**[13] | both GLAD-PC and the American Academy of Child and Adolescent Psychiatry concluded that medication be maintained for 6 to 12 months after the full resolution of depressive symptoms. [22, 90–93] |
| **VA/DoD 2016**[14] | In patients with MDD who achieve remission with antidepressant medication, we recommend continuation of antidepressants at the therapeutic dose for at least six months to decrease risk of relapse. [115-119]<br><br>Therefore, we recommend that continuation antidepressant treatment is continued for at least six months after a first episode of MDD. However, for patients who had two or more episodes of MDD, or belong to high risk subpopulations, antidepressants should be continued longer (see Maintenance Treatment Recommendations 16 and 17).<br><br>In patients at high risk for recurrent depressive episodes (see Discussion) and who are treated with pharmacotherapy, we recommend offering maintenance pharmacotherapy for at least 12 months and possibly indefinitely. [115,116, 120]<br><br>The patient should continue to take the medication even after feeling better. Most people need to be on medication for at least 6 to 12 months after adequate response to prevent relapses. |
| **WHO 2015+2016**[7] | Antidepressant medications usually need to be continued for at least 9-12 months after the resolution of symptoms. |
| **APA 2010**[8] | To reduce the risk of relapse, patients who have been treated successfully with antidepressant medications in the acute phase should continue treatment with these agents for 4–9 months.<br><br>Although the number of randomized controlled trials of antidepressant medications in the continuation phase is limited, the available data indicate that patients treated for a first episode of uncomplicated major depressive disorder who exhibit a satisfactory response to an antidepressant medication should continue to receive a full therapeutic dose of that agent for at least 4–9 months after achieving full remission. [105, 225, 495]<br><br>Continuation phase pharmacotherapy is strongly recommended following successful acute phase antidepressant therapy, with a recommended duration of continuation therapy of approximately 4–9 months (assuming good and consistent control of depression symptoms).<br><br>For many patients, particularly for those with chronic and recurrent major depressive disorder or co-occurring medical and/or psychiatric disorders, some form of maintenance treatment will be required indefinitely. |
| **NZGG + MoH 2008**[4] | Antidepressants should normally be continued for at least 6 months after remission, to reduce the risk of relapse.<br><br>Adults/pakeke taking antidepressants should normally continue to take them for at least 6 months after remission of a first episode of depression as this greatly reduces the risk of relapse. [354] After a second or subsequent episode, antidepressants should be continued for at least 2 years. [9] |
| **NICE 2019**[15] | When a child or young person responds to treatment with fluoxetine, medication should be continued for at least 6 months after remission (defined as no symptoms and full functioning for at least 8 weeks); in other words, for 6 months after this 8-week period. |

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| | When a child or young person responds to treatment with citalopram or sertraline, medication should be continued for at least 6 months after remission (defined as no symptoms and full functioning for at least 8 weeks). |
| **WFSBP 2007**[3] | Given the high rate of relapse of depression, continuation therapy is recommended for all children and adolescents for at least 6 months.<br><br>Three years of maintenance therapy is appropriate almost as a routine for patients with recurrences, particularly where an episode prior to the present one has occurred in the last 5 years or where remission has been difficult to achieve.<br><br>Maintenance treatment may last from 3 years to a lifetime. In general, the graver the prognosis, the longer the maintenance therapy should last.<br><br>Maintenance for over 5 years or indefinitely is recommended for those patients at greater risk, particularly where two or three attempts to withdraw medication have been followed by another episode within a year. |
| **AACAP 2007**[16] | Until further research becomes available, continuation therapy for at least 6 to 12 months is recommended for all patients who have responded to the acute treatment.<br><br>To Consolidate the Response to the Acute Treatment and Avoid Relapses, Treatment Should Always Be Continued for 6 to 12 Months.<br><br>To Avoid Recurrences, Some Depressed Children and Adolescents Should Be Maintained in Treatment for Longer Periods of Time.<br><br>As discussed in the Clinical Course section, MDD is a recurrent illness. Thus, once the child has been asymptomatic for approximately 6 to 12 months, the clinician must decide whether maintenance therapy is indicated and the type and duration of therapy. The main goal of the maintenance phase is to foster healthy growth and development and prevent recurrences. This phase may last 1 year or longer and is typically conducted with visits at a frequency of monthly to quarterly, depending on the patient's clinical status, functioning, support systems, environmental stressors, motivation for treatment, existence of comorbid psychiatric/medical disorders, and availability and skill of the clinician.<br><br>Specifically, those patients with at least two episodes of depression or one severe episode or chronic episodes of depression should have maintenance treatment for longer than 1 year.<br><br>Those with double depression (depression with comorbid DD) who have been depressed "as long as they can remember" may need treatment indefinitely, with an explanation to families that there is no hard-and-fast rule about this because of a lack of studies in this population. Moreover, other factors that are related to risk of a prolonged episode or recurrence should also make the clinician consider maintenance treatments. These factors include patient factors of comorbidity, psychosis, suicidality, number of prior episodes, environmental factors such as family disruption due to conditions external to the child (e.g., divorce, illness, job loss, homelessness), family psychopathology, and lack of community support. |
| **NICE 2009**[5] | Support and encourage a person who has benefited from taking an antidepressant to continue medication for at least 6 months after remission of an episode of depression.<br><br>Advise people with depression to continue antidepressants for at least 2 years if they are at risk of relapse. |
| **RCPSYCH 2003**[17] | In depressive episode, current evidence suggests acute treatment for at least six weeks and a continuation period of at least 12 months.<br><br>Patients with first onset depressive episode should be continued for a minimum of 12 months on the same dosage of antidepressant that got them well.<br><br>Those with recurrent depression should be continued at the same dosage that got them well for 12–36 months with a review held with the patient to discuss risk factors at regular intervals.<br><br>For high risk patients, treatment should be continued for a minimum of 3 years.<br><br>Acute treatment lasts at least 6 weeks and continuation treatment at least 12 months. |
| **MoH (SI) 2012**[18] | Patients with first episode of depression without psychotic symptoms should be treated with antidepressants at full treatment dose for 6-9 months after remission of symptoms. [73, 74]<br><br>Patients who have a second episode of depression should be maintained on treatment for 1-2 years - the duration may depend on the risk factors for recurrence and the patient preference. [75, 76]<br><br>Patients with more than two episodes of depression should be maintained on treatment for 2 years or longer, or even lifelong – the duration may depend on the risk factors for recurrence and the patient preference. [77, 78] |
| **NCCMH 2010**[6] | it is currently recommended that antidepressant drug treatment is continued for a minimum of 6 months after remission of major depression (12 months in older adults), and longer if there are factors that increase the risk of relapse.<br><br>Support and encourage a person who has benefited from taking an antidepressant to continue medication for at least 6 months after remission of an episode of depression. Discuss with the person that this greatly reduces the risk of relapse. |

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| | There is good evidence that patients with residual symptoms are at increasing risk of relapse of major depression and the current practice is to continue treatment for longer in those patients.<br><br>Advise people with depression to continue antidepressants for at least 2 years if they are at risk of relapse.<br><br>When deciding whether to continue maintenance treatment beyond 2 years, re-evaluate with the person with depression, taking into account age, comorbid conditions and other risk factors. |
| **Duration of tapering period** | |
| **BAP 2015**[9] | Take into account the clinical situation to determine the rate of taper; serious adverse events may warrant rapid discontinuation; otherwise a minimum period of 4 weeks taper is advised after longer-term treatment and a period of some months may be appropriate for planned treatment withdrawal after long-term prophylaxis. |
| **CANMAT 2016**[12] | Unless there are clinical reasons otherwise, we recommend slowly tapering the dose over several weeks when discontinuing antidepressants. |
| **WFSBP 2013 + 2015**[2] | Withdrawal of antidepressants and lithium, in particular after longer-term use (e.g., longer than 6 months), should always be gradual, with dose reductions over at least 3 months.<br><br>In clinical practice, antidepressants should always be withdrawn slowly after maintenance therapy. A tapering period of 4 – 6 months is recommended in long-term treated patients to allow the early detection of emerging symptoms and to minimize the risk of antidepressant medication discontinuation syndromes. |
| **WHO 2015+2016**[7] | Taper the dose of medication gradually, over a minimum of 4 weeks. Monitor the person for symptom recurrence. |
| **APA 2010**[8] | When pharmacotherapy is being discontinued, it is best to taper the medication over the course of at least several weeks.<br><br>Discontinuation syndromes have been found to be more frequent after discontinuation of medications with shorter half-lives, and patients maintained on short-acting agents should have their medications tapered gradually over a longer period. [518, 519]<br><br>Selective serotonin reuptake inhibitors generally should not be abruptly discontinued after extended therapy and, whenever possible, should be tapered over several weeks to minimize discontinuation-emergent symptoms |
| **NZGG + MoH 2008**[4] | Antidepressants should normally be withdrawn over a 4-week period. [65] |
| **NICE 2019**[15] | Where antidepressant medication is to be discontinued, the drug should be phased out over a period of 6 to 12 weeks with the exact dose being titrated against the level of discontinuation/withdrawal symptoms. |
| **WFSBP 2007**[3] | In clinical practice, antidepressants should always be tapered off slowly over a 4-6-month period after long-term maintenance therapy to allow the early detection of emerging symptoms and to minimize the risk of discontinuation syndromes.<br><br>At the end of the continuation phase, for patients who do not require maintenance treatment, medications should be discontinued gradually over a period of at least 6 weeks. |
| **NICE 2009**[5] | When stopping an antidepressant, gradually reduce the dose, normally over a 4-week period, although some people may require longer periods, particularly with drugs with a shorter half life (such as paroxetine and venlafaxine). This is not required with fluoxetine because of its long half-life. |
| **NCCMH 2010**[6] | When stopping an antidepressant, gradually reduce the dose, normally over a 4-week period, although some people may require longer periods, particularly with drugs with a shorter half-life (such as paroxetine and venlafaxine). This is not required with fluoxetine because of its long half-life.<br><br>Patients receiving MAOIs may need dosage to be tapered over a longer period.<br><br>Many patients experience discontinuation symptoms despite a slow taper. For these patients, the option of abrupt withdrawal should be discussed. Some may prefer a short period of intense symptoms over a prolonged period of milder symptoms. |
| **MoH (SI) 2012**[18] | Reduce over 4 weeks or longer for Paroxetine and Venlafaxine. Fluoxetine dose of 20mgs can be abruptly stopped and doses of above 20mgs recommended to reduce over a period of 2 weeks. |
| **RANZCP 2020**[10] | it is recommended that the dose of antidepressant be reduced slowly |
| **AAP 2018**[13] | In addition, all SSRIs should be slowly tapered when discontinued because of risk of withdrawal effects. |
| **VA/DoD 2016**[14] | Discontinuation of antidepressant therapy should be done with a slow taper since withdrawal done too rapidly may result in adverse withdrawal symptoms or return of the original depressive symptoms. Tapering should be guided by the elimination half-life of the medication and by close monitoring of the depressive symptoms. |
| **AACAP 2007**[16] | After the continuation or maintenance phases are over, or when the antidepressants need to be discontinued, all antidepressants, except for fluoxetine, should be discontinued slowly. Fluoxetine, because of its long half-life, is the exception and can be stopped at once. |
| **Dose-reduction regimen (specific dose-reductions in mg)** | |
| **MoH (SI) 2012**[18] | Abrupt cessation of antidepressant medication for women with preexisting depression can precipitate withdrawal symptoms that can be distressing. It is preferable to advise patients to reduce antidepressant dose to half first whilst arranging for referral. [155, 158] |

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| **RANZCP 2020**[10] | We suggest that, for those with risk factors for severe DaWS, the first step is to reduce the dose to the minimal effective dose. Following this, the dose should be halved, and after a week, the dose should be reduced more slowly in small decrements (allowing 2 weeks for each dose reduction), according to how the tablet can be divided. Unfortunately, this is not feasible with medications that are encapsulated (e.g. venlafaxine and duloxetine).<br><br>The dose of AD should be tapered down with the dose lowered generally in at least weekly steps, and the rate of stepping down the dose needs to be tailored to the individual patient (a) Initially, titrate down to the recommended minimum effective dose of the antidepressant (b) Once minimum effective dose is achieved, reduce the dose by no more than 50% weekly<br><br>It has recently been suggested that antidepressants should be tapered down hyperbolically (by lowering the dose by smaller amounts over time) in the same manner as benzodiazepines (Horowitz and Taylor, 2019), which is further supported by a Dutch taskforce (Ruhe et al., 2019). However, reducing the antidepressant in such a way is impractical as current preparations of antidepressant do not allow for the dose to be reduced by such small decrements.<br><br>For patients with one or more risk factors for withdrawal and discontinuation symptoms (treatment at higher than usual dose, long-term period on antidepressant, previous discontinuation and withdrawal symptoms or symptoms emerging with missed dose(s)), a slower taper is recommended. (a) Initially, drop to the recommended minimum effective dose of the antidepressant (b) Reduce the dose by small decrements (dependent on how the tablets can be cut up) every 2 weeks |
| **Whether the guideline suggests a gradual dose-reduction** | |
| **BAP 2015**[9] | … otherwise a minimum period of 4 weeks taper is advised. |
| **RANZCP 2020**[10] | As DaWS occur following abrupt discontinuation of the antidepressant, it is recommended that the dose of antidepressant be reduced slowly. |
| **CANMAT 2016**[12] | Unless there are clinical reasons otherwise, we recommend slowly tapering the dose over several weeks when discontinuing antidepressants. |
| **WFSBP 2013 + 2015**[2] | If no relapse occurs during continuation therapy, a gradual discontinuation of the antidepressant medication is recommended in case of first episodes. [Rosenbaum 1998]<br><br>Withdrawal of antidepressants and lithium, in particular after longer-term use (e.g., longer than 6 months), should always be gradual, with dose reductions over at least 3 months. |
| **AAP 2018**[13] | all SSRIs should be slowly tapered when discontinued. |
| **VA/DoD 2016**[14] | Discontinuation of antidepressant therapy should be done with a slow taper since withdrawal done too rapidly may result in adverse withdrawal symptoms or return of the original depressive symptoms. Tapering should be guided by the elimination half-life of the medication and by close monitoring of the depressive symptoms. |
| **WHO 2015-2016**[7] | Taper the dose of medication gradually, over a minimum of 4 weeks. Monitor the person for symptom recurrence. |
| **APA 2010**[8] | To minimize the likelihood of discontinuation symptoms, patients should be advised not to stop medications abruptly and to take medications with them when they travel or are away from home.<br><br>When pharmacotherapy is being discontinued, it is best to taper the medication over the course of at least several weeks.<br><br>A slow taper or temporary change to a longer half-life antidepressant may reduce the risk of discontinuation syndrome when discontinuing antidepressants or reducing antidepressant doses.<br><br>Selective serotonin reuptake inhibitors generally should not be abruptly discontinued after extended therapy and, whenever possible, should be tapered over several weeks to minimize discontinuation-emergent symptoms. |
| **NZGG + MoH 2008**[4] | Antidepressants should normally be withdrawn over a 4-week period. |
| **NICE 2019**[15] | Where antidepressant medication is to be discontinued, the drug should be phased out over a period of 6 to 12 weeks with the exact dose being titrated against the level of discontinuation/withdrawal symptoms. |
| **WFSBP 2007**[3] | If no relapse occurs during continuation therapy, a gradual discontinuation of the antidepressant medication is recommended. [Rosenbaum et al. 1998]<br><br>In clinical practice, antidepressants should always be tapered off slowly over a 4-6-month period after long-term maintenance therapy to allow the early detection of emerging symptoms and to minimize the risk of discontinuation syndromes.<br><br>At the end of the continuation phase, for patients who do not require maintenance treatment, medications should be discontinued gradually over a period of at least 6 weeks.<br><br>In the case of only partial or non-response, gradual dose reduction under close observation is an option. Abrupt discontinuation of the medication must be avoided. |
| **AACAP 2007**[16] | After the continuation or maintenance phases are over, or when the antidepressants need to be discontinued, all antidepressants, except for fluoxetine, should be discontinued slowly. Fluoxetine, because of its long half-life, is the exception and can be stopped at once.<br><br>Abrupt discontinuation of antidepressants may induce withdrawal symptoms, some of which may mimic a relapse or recurrence of a depressive episode (e.g., tiredness, irritability, severe somatic symptoms [Zajecka et al., 1997]). |

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| **NICE 2009**[5] | When stopping an antidepressant, gradually reduce the dose, normally over a 4-week period, although some people may require longer periods, particularly with drugs with a shorter half life (such as paroxetine and venlafaxine). This is not required with fluoxetine because of its long half-life. |
| **MoH (SI) 2012**[18] | When discontinuing antidepressants, antidepressants should be gradually tapered off instead of suddenly stopped, to reduce side effects of discontinuation. [89,90]<br><br>Abrupt cessation of antidepressant medication for women with preexisting depression can precipitate withdrawal symptoms that can be distressing. It is preferable to advise patients to reduce antidepressant dose to half first whilst arranging for referral. [155, 158]<br><br>Reduce over 4 weeks or longer for Paroxetine and Venlafaxine. Fluoxetine dose of 20mgs can be abruptly stopped and doses of above 20mgs recommended to reduce over a period of 2 weeks. |
| **NCCMH 2010**[6] | When stopping an antidepressant, gradually reduce the dose, normally over a 4-week period, although some people may require longer periods, particularly with drugs with a shorter half-life (such as paroxetine and venlafaxine). |
| **Whether the guideline suggests a linear tapering regimen (Y/N)** | |
| **MoH (SI) 2012**[18] | Abrupt cessation of antidepressant medication for women with preexisting depression can precipitate withdrawal symptoms that can be distressing. It is preferable to advise patients to reduce antidepressant dose to half first whilst arranging for referral. |
| **Whether the guideline suggests a hyperbolic tapering regimen (Y/N)** | |
| **NCCMH 2010**[6] | The end of the taper may need to be slower as symptoms may not appear until the reduction in the total daily dosage of the antidepressant is substantial. |
| **RANZCP 2020**[10] | For patients with one or more risk factors for withdrawal and discontinuation symptoms (treatment at higher than usual dose, long-term period on antidepressant, previous discontinuation and withdrawal symptoms or symptoms emerging with missed dose(s)), a slower taper is recommended. (a) Initially, drop to the recommended minimum effective dose of the antidepressant (b) Reduce the dose by small decrements (dependent on how the tablets can be cut up) every 2 weeks |
| **Actions if discontinuation symptoms emerge** | |
| **BAP 2015**[9] | If a discontinuation reaction does occur: 1) explanation and reassurance are often all that is required, 2) if this is not sufficient, and for more severe reactions, the antidepressant should be restarted and tapered more slowly; for SSRIs and serotonin and noradrenaline reuptake inhibitors (SNRIs) consider switching to fluoxetine which can then be stopped after discontinuation symptoms have fully subsided. |
| **APA 2010**[8] | The psychiatrist should closely monitor patients withdrawing from antidepressants and provide reassurance that symptoms are time-limited and can be addressed by more gradual tapering.<br><br>Another strategy is to change to a brief course of fluoxetine, e.g., 10 mg for 1–2 weeks, and then discontinue the fluoxetine. [165] |
| **NZGG + MoH 2008**[4] | If symptoms are severe, the patient may need to resume taking the antidepressant and reduce it more slowly. [65] |
| **NICE 2019**[15] | Where antidepressant medication is to be discontinued, the drug should be phased out over a period of 6 to 12 weeks with the exact dose being titrated against the level of discontinuation/withdrawal symptoms. |
| **NICE 2009**[5] | Inform the person that they should seek advice from their practitioner if they experience significant discontinuation symptoms. If discontinuation symptoms occur: 1) monitor symptoms and reassure the person if symptoms are mild 2) consider reintroducing the original antidepressant at the dose that was effective (or another antidepressant with a longer half-life from the same class) if symptoms are severe, and reduce the dose gradually while monitoring symptoms. |
| **NCCMH 2010**[6] | Inform the person that they should seek advice from their practitioner if they experience significant discontinuation symptoms. If discontinuation symptoms occur: 1) monitor symptoms and reassure the person if symptoms are mild 2) consider reintroducing the original antidepressant at the dose that was effective (or another antidepressant with a longer half-life from the same class) if symptoms are severe, and reduce the dose gradually while monitoring symptoms. [Haddad, 2001; Lejoyeux & Ades, 1997]<br><br>If symptoms are mild, reassure the patient that these symptoms are not uncommon after discontinuing an antidepressant and that they will pass in a few days. If symptoms are severe, reintroduce the original antidepressant (or another with a longer half-life from the same class) and taper gradually while monitoring for symptoms. [Haddad, 2001; Lejoyeux & Ades, 1997]<br><br>Many patients experience discontinuation symptoms despite a slow taper. For these patients, the option of abrupt withdrawal should be discussed. Some may prefer a short period of intense symptoms over a prolonged period of milder symptoms. |
| **Actions if deterioration/relapse occurs (including any indications that symptoms arising when stopping antide pressants is interpreted as relapse + how to manage)** | |
| **BAP 2015**[9] | Treatment of relapse while on continuation therapy: If antidepressants have been stopped re-start the patient on an antidepressant at adequate dose; if the dose had been lowered re-establish the previous dose. |
| **WFSBP 2013 + 2015**[2] | If tapering off results in a return of symptoms, the medication should be re-instated in the original dose for at least another 6 months before attempting discontinuation again.<br><br>When symptoms return during or after withdrawal of lithium or antidepressants, full-dose maintenance treatment should be resumed. |

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| | If the full depressive episode recurs during or after discontinuation, a full therapeutic dosage should be promptly re-administered. [AHCPR 1993] |
| **APA 2010**[8] | Before the discontinuation of active treatment, patients should be informed of the potential for a depressive relapse and a plan should be established for seeking treatment in the event of recurrent symptoms. After discontinuation of medications, patients should continue to be monitored over the next several months and should receive another course of adequate acute phase treatment if symptoms recur.<br><br>If a patient does suffer a recurrence after discontinuing medication, treatment should be promptly reinitiated. Usually, the previous treatment regimen to which the patient responded in the acute and continuation phases should be reinitiated. [520] Patients who have a recurrence following discontinuation of antidepressant therapy should be considered to have experienced another major depressive disorder episode and should receive adequate acute-phase treatment followed by continuation-phase treatment and possibly maintenance-phase treatment.<br><br>When pharmacotherapy is being discontinued, it is best to taper the medication over the course of at least several weeks. Such tapering allows for the detection of recurring symptoms at a time when patients are still partially treated and therefore more easily returned to full therapeutic treatment if needed. In addition, such tapering can help minimize the incidence of antidepressant medication discontinuation syndromes, particularly with paroxetine and venlafaxine. [98, 163, 164] Discontinuation syndromes are problematic because their symptoms include disturbances of mood, energy, sleep, and appetite and can therefore be mistaken for or mask signs of relapse. [517]<br><br>Patients should be carefully monitored during and immediately after treatment discontinuation to ensure that remission is stable. |
| **WFSBP 2007**[3] | If tapering off results in a return of symptoms, the medication in the original dose should be continued for at least another 6 months before attempting discontinuation again.<br><br>If the full depressive episode recurs during or after discontinuation, the full therapeutic dosage should be promptly readministered. [AHCPR 1993] Regardless of the reason for the point in time at which longterm pharmacotherapy is discontinued, the patient should be educated about the risk of recurrence and its early warning signs. |
| **Mention of potential benefits and harms associated with stopping or tapering antidepressants** | |
| **BAP 2015**[9] | When stopping antidepressant treatment after a period of prophylaxis, match the timing to both risk and consequences of relapse and warn the patient that the highest period of risk is in the 6 months after stopping.<br><br>A factor that may not be considered is the consequence of relapse if antidepressants are stopped at a critical time in a person's life (e.g. examinations, etc), given that the highest risk of relapse is in the 6 months after stopping (see above).<br><br>Be aware of the characteristic symptoms of a discontinuation reaction and its possibility in any patient who stops antidepressant drug treatment.<br><br>Discontinuation symptoms may occur on abruptly stopping all classes of antidepressants, with differences seen between classes of drugs.<br><br>Acute discontinuation symptoms have been described with all of the main classes of antidepressants including TCAs, MAOIs, SSRIs, SNRIs and mirtazapine (see reviews by Haddad and Anderson, 2007; Howland, 2010). [Haddad and Anderson, 2007; Howland, 2010] |
| **RANZCP 2020**[10] | Inform patients when starting on an antidepressant that they may experience discontinuation and withdrawal symptoms and should not stop antidepressants abruptly and should discuss stopping their antidepressant with their treating physician |
| **WFSBP 2013 + 2015**[2] | Regardless of the reason when long-term pharmacotherapy is discontinued, the patient should be educated about the risk of recurrence and its early warning signs. Three phenomena that may occur after discontinuing long-term antidepressant medications need to be distinguished: recurrence of episode (return of the original symptoms), rebound (return of original symptoms but with greater intensity; typically occurs if lithium is withdrawn too rapidly), and withdrawal (development of different symptoms related to drug stoppage; typically occurs if TCAs, SSRIs or venlafaxine are abruptly stopped). [Paykel 2001]<br><br>During the period of discontinuation, the patient should be monitored more closely. After discontinuation is complete monitoring should continue during the next couple of months (e.g., particularly for the next 6 months, which appear to be a period of high risk for recurrence to identify those in whom a relapse/recurrence is likely). [Lam 2009]<br><br>With longer use of most antidepressants, stepdown discontinuation within a period of 1 – 4 weeks is recommended rather than abrupt discontinuation, as this may cause discontinuation symptoms. |
| **AAP 2018**[13] | In addition, Emslie et al [93] found the greatest risk of relapse to be in the first 8 to 12 weeks after discontinuing medication, which suggests that after stopping an antidepressant, close follow-up should be encouraged for at least 2 to 3 months. Other studies have revealed similar benefits of prolonged treatment after acute response. [90 –93]<br><br>In addition, all SSRIs should be slowly tapered when discontinued because of risk of withdrawal effects. |
| **VA/DoD 2016**[14] | Discontinuation of antidepressant therapy should be done with a slow taper since withdrawal done too rapidly may result in adverse withdrawal symptoms or return of the original depressive symptoms. |

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| | Tapering should be guided by the elimination half-life of the medication and by close monitoring of the depressive symptoms. |
| **APA 2010**[8] | Before the discontinuation of active treatment, patients should be informed of the potential for a depressive relapse and a plan should be established for seeking treatment in the event of recurrent symptoms. After discontinuation of medications, patients should continue to be monitored over the next several months and should receive another course of adequate acute phase treatment if symptoms recur.<br><br>If a patient does suffer a recurrence after discontinuing medication, treatment should be promptly reinitiated. Usually, the previous treatment regimen to which the patient responded in the acute and continuation phases should be reinitiated (520). [520] Patients who have a recurrence following discontinuation of antidepressant therapy should be considered to have experienced another major depressive disorder episode and should receive adequate acute-phase treatment followed by continuation-phase treatment and possibly maintenance-phase treatment.<br><br>When pharmacotherapy is being discontinued, it is best to taper the medication over the course of at least several weeks. Such tapering allows for the detection of recurring symptoms at a time when patients are still partially treated and therefore more easily returned to full therapeutic treatment if needed.<br><br>To minimize the likelihood of discontinuation symptoms, patients should be advised not to stop medications abruptly and to take medications with them when they travel or are away from home.<br><br>Patients should be carefully monitored during and immediately after treatment discontinuation to ensure that remission is stable. The highest risk for a relapse is seen in the first 2 months after discontinuation of treatment.<br><br>In addition, such tapering can help minimize the incidence of antidepressant medication discontinuation syndromes, particularly with paroxetine and venlafaxine. [98, 163, 164] |
| **NZGG + MoH 2008**[4] | Unplanned conception for a woman on antidepressants may prompt her to abruptly stop taking the medication, incurring high risk of recurrence of depression before delivery. [475] Careful reassessment of risks will help women to decide whether continuation of antidepressants is appropriate. [453]<br><br>Discontinuation symptoms may occur if the drugs are suddenly stopped, doses are missed or (occasionally) the dose is reduced. [ii]<br><br>Patients should be warned that they may experience withdrawal symptoms, which are usually mild and self-limiting.<br><br>If considering a dose reduction, the practitioner should be aware that women taking paroxetine and venlafaxine could experience withdrawal or discontinuation side effects when reducing the dose, due to the short half-life of these drugs. |
| **WFSBP 2007**[3] | Regardless of the reason for the point in time at which long-term pharmacotherapy is discontinued, the patient should be educated about the risk of recurrence and its early warning signs.<br><br>In clinical practice, antidepressants should always be tapered off slowly over a 4-6-month period after long-term maintenance therapy to allow the early detection of emerging symptoms and to minimize the risk of discontinuation syndromes.<br><br>During the period of discontinuation, the patient should be closely monitored. To identify those in whom a relapse is likely after the discontinuation is completed, the monitoring should continue for the next few months (e.g., particularly for the next 6 months, which appear to be a period of high risk for recurrence [Rush and Kupfer 2001]).<br><br>Discontinuation symptoms after abrupt antidepressant cessation have been reported for all drug classes.<br><br>With longer use of most antidepressants stepdown discontinuation within a period of 1_2 weeks is recommended rather than abrupt discontinuation, for this may cause withdrawal symptoms. Patients should be carefully monitored during and immediately after discontinuation to ensure the stability of the remission. [American Psychiatric Association 2000] |
| **AACAP 2007**[16] | Often discontinuation can be tried during the summer, so that a relapse would be less disruptive to school function; however, it is important to note that the treatment for depression can also be helping other disorders (e.g., anxiety) and discontinuation may accelerate the symptoms of these other conditions.<br><br>Some studies have reported that the half-lives of sertraline, citalopram, paroxetine, and bupropion SR are much shorter than reported in adults. [Axelson et al., 2002, Daviss et al., 2005; Findling et al., 2006] Therefore, psychiatrists should be alert for the possibility of withdrawal side effects when these medications are prescribed once daily.<br><br>Abrupt discontinuation of antidepressants may induce withdrawal symptoms, some of which may mimic a relapse or recurrence of a depressive episode (e.g., tiredness, irritability, severe somatic symptoms).<br><br>Continuation treatment is required for all depressed youths to consolidate the response during the acute phase and avoid relapses. |
| **NICE 2009**[5] | Support and encourage a person who has benefited from taking an antidepressant to continue medication for at least 6 months after remission of an episode of depression. Discuss with the person that this greatly reduces the risk of relapse. |

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| | For people with depression who are at significant risk of relapse or have a history of recurrent depression, discuss with the person treatments to reduce the risk of recurrence, including continuing medication.<br><br>Advise people that if they stop taking antidepressant medication abruptly, miss doses or do not take a full dose, they may have discontinuation symptoms such as… |
| **MoH (SI) 2012**[18] | For women with pre-existing depressive illness: Consider risk of relapse as high as 70% if antidepressants stopped. [158]<br><br>When discontinuing antidepressants, antidepressants should be gradually tapered off instead of suddenly stopped, to reduce side effects of discontinuation. [89,90]<br><br>Discontinuation symptoms may occur after missed doses if the antidepressant prescribed has a short half life. [75]<br><br>Abrupt cessation of antidepressant medication for women with preexisting depression can precipitate withdrawal symptoms that can be distressing. [155, 158] |
| **NCCMH 2010**[6] | Support and encourage a person who has benefited from taking an antidepressant to continue medication for at least 6 months after remission of an episode of depression. Discuss with the person that: 1) this greatly reduces the risk of relapse.<br><br>Advise people with depression who are taking antidepressants that discontinuation symptoms [179] may occur on stopping, missing doses or, occasionally, on reducing the dose of the drug. Explain that symptoms are usually mild and self-limiting over about 1 week, but can be severe, particularly if the drug is stopped abruptly. |
| **SIGN + HIS 2012**[1] | … be aware of the need for close monitoring for change in mental state where a woman decides to cease her usual medication. Stopping medication may lead to relapse of illness. |
| **WHO 2015+2016**[7] | Taper the dose of medication gradually, over a minimum of 4 weeks. Monitor the person for symptom recurrence. |
| **HSE + ICGP 2006**[11] | Discuss the patient's fears of addiction and inform about risk of discontinuation symptoms (particularly associated with some of the SSRI and SNRI)… |
| **CANMAT 2016**[12] | Discontinuation symptoms, described by the FINISH mnemonic (flu-like symptoms, insomnia, nausea, imbalance, sensory disturbances, hyperarousal), may be experienced by up to 40% of patients when antidepressants are stopped abruptly. [87,88] |
| **NICE 2019**[15] | Where antidepressant medication is to be discontinued, the drug should be phased out over a period of 6 to 12 weeks with the exact dose being titrated against the level of discontinuation/withdrawal symptoms. |
| **WFSBP 2013 + 2015**[2] | Regardless of the reason when long-term pharmacotherapy is discontinued, the patient should be educated about the risk of recurrence and its early warning signs. Three phenomena that may occur after discontinuing long-term antidepressant medications need to be distinguished: recurrence of episode (return of the original symptoms), rebound (return of original symptoms but with greater intensity; typically occurs if lithium is withdrawn too rapidly), and withdrawal (development of different symptoms related to drug stoppage; typically occurs if TCAs, SSRIs or venlafaxine are abruptly stopped). [Paykel 2001] |
| **Mention of confounding discontinuation symptoms with relapse** | |
| **BAP 2015**[9] | In most patients discontinuation symptoms are self-limiting and of short duration, but in a minority of cases they can be severe and last several weeks, and there is the potential for misdiagnosis as relapse as depressive symptoms do occur. [Haddad and Anderson, 2007; Tint et al., 2008] |
| **AACAP 2007**[16] | Abrupt discontinuation of antidepressants may induce withdrawal symptoms, some of which may mimic a relapse or recurrence of a depressive episode (e.g., tiredness, irritability, severe somatic symptoms [Zajecka et al., 1997]). |
| **APA 2010**[8] | When pharmacotherapy is being discontinued, it is best to taper the medication over the course of at least several weeks. Such tapering allows for the detection of recurring symptoms at a time when patients are still partially treated and therefore more easily returned to full therapeutic treatment if needed. In addition, such tapering can help minimize the incidence of antidepressant medication discontinuation syndromes, particularly with paroxetine and venlafaxine. [98, 163, 164] Discontinuation syndromes are problematic because their symptoms include disturbances of mood, energy, sleep, and appetite and can therefore be mistaken for or mask signs of relapse. [517] |
| **NCCMH 2010**[6] | Discontinuation symptoms can be broadly divided into six groups; affective (for example, irritability), gastrointestinal (for example, nausea), neuromotor (for example, ataxia), vasomotor (for example, sweating), neurosensory (for example, paraesthesia), and other neurological (for example, dreaming; [Delgrado, 2006]). They may be new or hard to distinguish from some of the original symptoms of the underlying illness.<br><br>The symptoms of a discontinuation reaction may be mistaken for a relapse of illness or the emergence of a new physical illness, [Haddad, 2001] leading to unnecessary investigations or reintroduction of the antidepressant.<br><br>It is very important to counsel patients before, during and after antidepressant treatment about the nature of this syndrome.<br><br>Discontinuation symptoms may also be more common in those who relapse on stopping antidepressants. [Zajecka et al., 1998; Markowitz et al., 2000] |

**Supplementary Table 4.** AGREE II assessment details.

The *Scope and purpose* domain evaluates whether the overall objective(s), health questions and intents, expected benefits, and target patient populations are specifically described. The mean score for the domain was 62% (range 31-94%; SD 20). Common reasons for low ratings were lack of specificity and visibility of the information, primarily regarding the health questions and intents (e.g., diagnosis, treatment, screening, prevention) and descriptions of target patient population (e.g., excluded populations, comorbidities, differential diagnosis, and clinical condition). Many guidelines lacked an explicit introducing statement and provided only generic information in the body text.

The *Stakeholder involvement* domain evaluates whether appropriate stakeholders and intended users were involved in the guideline development group, including ideally all relevant professional groups, patients, and clinicians. The mean score for the domain was 42% (range 3-83%; SD 23). Two main issues contributed to the low scores in this domain. One concerned patient involvement; the few CPGs that did include patients in the development process did not describe their actual role and impact on the guidance. None of the CPGs sought the patients' views by considering evidence from surveys or focus groups, and guidance on stopping and tapering was not informed by patients' views and preferences. The other main issue was a seemingly overrepresentation of medical professionals in the guideline development groups, and thus a general low representation of other relevant professional groups, e.g., clinical psychologists, nurses, social workers, researchers, and methodologists. Furthermore, while the target users of the CPGs were generally well described, the individual members' role and impact when developing the CPG were rarely described. Some guidelines provided no information on this domain.

The *Rigor of development* domain addresses methods related to searching for and selecting the evidence, grading the evidence, and the process of translating the synthesized evidence into guidance. The mean score for the domain was 27% (range 0-50%; SD 12). The methods used to formulate the recommendations from the evidence were not described in any CPG. Some mentioned that 'consensus was used' or that they 'met to discuss' but contained no details on how the members agreed (e.g., delphi techniques, voting procedures, areas of disagreement and methods for resolving them, and outcomes of such procedures). In none of the CPGs did we find an assessment of the risk of bias pertaining to supporting studies or of the certainty of the evidence supporting the guidance on stopping or tapering antidepressants. Systematic literature searches were generally used, but sufficient information to replicate the search was only provided in about half of the CPGs (e.g., databases, search strategy and terms, inclusion and exclusion criteria, time periods searched). Most recommendations had no references to supporting evidence, and the references that were provided often seemed either irrelevant to the recommendation or were references to other CPGs. When no evidence or low-quality evidence was used, this was rarely mentioned in the CPG, and study limitations were generally not considered when formulating the recommendations. When discussing discontinuation and how long treatment should continue, no health benefits of coming off antidepressants were considered as relevant factors, whereas harms (withdrawal symptoms and relapse) were generally well considered. Consequently, no trade-off assessment between benefits and harms was considered. Finally, a statement on the procedures for updating the CPG was provided in only three (14%) CPGs,[1–3] planning an update after two,[3] three,[1] and five years[2] from the year of publication. None of these planned updates could be found.

The *Clarity of presentation* domain covers the degree to which recommendations are specific, unambiguous, and easily identifiable, including whether different options for managing the condition are presented. The mean score for the domain was 21% (range 0-39%; SD 10). Recommendations were generally vague, subjective, and open to interpretation, e.g., tapering 'slower' or 'over a longer/extended period of time'; 'provide reassurance'; 'seek advice from practitioner'; and the general issue of not providing actual statements on recommended actions, specifically regarding the end of maintenance treatment and what a gradual taper means in terms of dose reductions. Different options for managing withdrawal symptoms were rarely provided; such guidance pertained to resuming the antidepressant, starting another antidepressant, tapering 'more slowly', monitoring symptoms, or providing explanation or reassurance, but not to help patients cope with the symptoms and get through them. The recommendations are likely difficult for clinicians to comply with in practice, as very little concrete guidance was provided. The guidance on tapering and discontinuing antidepressants was rarely located under appropriate headlines or grouped in sections to identify it easily. Most recommendations were located in the body text. Most guidelines included a treatment algorithm or flow chart to illustrate the overall treatment plan, but in none of the CPGs did these include the discontinuation phase of treatment.

The *Applicability* domain evaluates whether potential facilitators and barriers to the application of the CPG were considered, including potential resource implications; auditing criteria; and advice on how to put the recommendations in to practice. The mean score for the domain was 6% (range 0-27%; SD 8). None of these aspects were adequately covered in any of the CPGs; only a few CPGs mentioned some of the aspects in generic terms, but no information to clinicians on how to implement the discontinuation phase of treatment in clinical practice was provided.

The *Editorial independence* domain addresses potential funding issues and conflicts of interests of guideline development members. The mean score for the domain was 30% (range 0-71%; SD 22). Generally, the CPGs provided insufficient information to ascertain the degree of editorial independence. Main issues were lack of explicit statement that the funding body did not influence the guideline content, details on how the guideline development group addressed potential influence from the funding body, information about how conflicts of interest were sought and defined, how they were dealt with when found, how the influence of competing interests were sought minimized, and incomplete reporting of conflicts of interest for all authors. Most guidelines provided no information on this domain, whereas some guidelines provided flawless and detailed information.

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AGREE II

# A critical group appraisal of: APA 2010. Practice guideline for the treatment of patients with major depressive disorder Third Edition using the AGREE II Instrument

Created with the AGREE II Online Guideline Appraisal Tool.

No endorsement of the content of this document by the AGREE Research Trust should be implied.

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Date: 10 June 2021

URL of this appraisal: http://www.agreetrust.org/group-appraisal/14573

Guideline URL:

| Domain 1 | Domain 2 | Domain 3 | Domain 4 | Domain 5 | Domain 6 | OA 1 | OA 2 |
|---|---|---|---|---|---|---|---|
| 42% | 11% | 27% | 19% | 0% | 38% | 25% | Yes - 0, Yes with modifications - 0, No - 2 |

| *Domain 1. Scope and Purpose* | | |
|---|---|---|
| | Appraiser 2 | Appraiser 1 |
| Item 1 | 3 | 4 |
| Item 2 | 3 | 2 |
| Item 3 | 5 | 4 |
| | | |
| *Domain 2. Stakeholder Involvement* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 4 | 1 | 2 |
| Item 5 | 1 | 2 |
| Item 6 | 2 | 2 |
| | | |
| *Domain 3. Rigour of Development* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 7 | 4 | 4 |
| Item 8 | 2 | 2 |
| Item 9 | 2 | 2 |
| Item 10 | 5 | 6 |
| Item 11 | 2 | 2 |
| Item 12 | 1 | 1 |
| Item 13 | 4 | 3 |
| Item 14 | 1 | 1 |
| | | |
| *Domain 4. Clarity of Presentation* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 15 | 2 | 3 |
| Item 16 | 3 | 3 |
| Item 17 | 1 | 1 |
| | | |
| *Domain 5. Applicability* | | |
| | Appraiser 2 | Appraiser 1 |

| | | |
|---|---|---|
| Item 18 | 1 | 1 |
| Item 19 | 1 | 1 |
| Item 20 | 1 | 1 |
| Item 21 | 1 | 1 |
| | | |
| *Domain 6. Editorial Independence* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 22 | 2 | 2 |
| Item 23 | 5 | 4 |
| | | |
| *Overall Assessment* | | |
| | Appraiser 2 | Appraiser 1 |
| OA1 | 2 | 3 |

Created online at www.agreetrust.org 10 June 2021


AGREE II

# A critical group appraisal of: BAP 2015. Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology guidelines using the AGREE II Instrument

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URL of this appraisal: http://www.agreetrust.org/group-appraisal/14430

Guideline URL:

| Domain 1 | Domain 2 | Domain 3 | Domain 4 | Domain 5 | Domain 6 | OA 1 | OA 2 |
|---|---|---|---|---|---|---|---|
| 67% | 56% | 13% | 28% | 0% | 33% | 17% | Yes - 0, Yes with modifications - 0, No - 1 |

| *Domain 1. Scope and Purpose* | |
|---|---|
| | Appraiser 2 |
| Item 1 | 6 |
| Item 2 | 4 |
| Item 3 | 5 |
| | |
| *Domain 2. Stakeholder Involvement* | |
| | Appraiser 2 |
| Item 4 | 4 |
| Item 5 | 3 |
| Item 6 | 6 |
| | |
| *Domain 3. Rigour of Development* | |
| | Appraiser 2 |
| Item 7 | 2 |
| Item 8 | 1 |
| Item 9 | 2 |
| Item 10 | 2 |
| Item 11 | 2 |
| Item 12 | 2 |
| Item 13 | 2 |
| Item 14 | 1 |
| | |
| *Domain 4. Clarity of Presentation* | |
| | Appraiser 2 |
| Item 15 | 3 |
| Item 16 | 2 |
| Item 17 | 3 |
| | |
| *Domain 5. Applicability* | |
| | Appraiser 2 |

| | |
|---|---|
| Item 18 | 1 |
| Item 19 | 1 |
| Item 20 | 1 |
| Item 21 | 1 |
| | |
| *Domain 6. Editorial Independence* | |
| | Appraiser 2 |
| Item 22 | 4 |
| Item 23 | 2 |
| | |
| *Overall Assessment* | |
| | Appraiser 2 |
| OA1 | 2 |

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# A critical group appraisal of: HSE + ICGP 2006. Guidelines for the management of depression and anxiety disorders in primary care using the AGREE II Instrument

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URL of this appraisal: http://www.agreetrust.org/group-appraisal/14566

Guideline URL:

| Domain 1 | Domain 2 | Domain 3 | Domain 4 | Domain 5 | Domain 6 | OA 1 | OA 2 |
|---|---|---|---|---|---|---|---|
| 31% | 25% | 0% | 8% | 0% | 0% | 8% | Yes - 0, Yes with modifications - 0, No - 2 |

| *Domain 1. Scope and Purpose* | | |
|---|---|---|
| | Appraiser 2 | Appraiser 1 |
| Item 1 | 3 | 2 |
| Item 2 | 3 | 3 |
| Item 3 | 3 | 3 |
| | | |
| *Domain 2. Stakeholder Involvement* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 4 | 2 | 2 |
| Item 5 | 1 | 1 |
| Item 6 | 5 | 4 |
| | | |
| *Domain 3. Rigour of Development* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 7 | 1 | 1 |
| Item 8 | 1 | 1 |
| Item 9 | 1 | 1 |
| Item 10 | 1 | 1 |
| Item 11 | 1 | 1 |
| Item 12 | 1 | 1 |
| Item 13 | 1 | 1 |
| Item 14 | 1 | 1 |
| | | |
| *Domain 4. Clarity of Presentation* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 15 | 2 | 2 |
| Item 16 | 1 | 2 |
| Item 17 | 1 | 1 |
| | | |
| *Domain 5. Applicability* | | |
| | Appraiser 2 | Appraiser 1 |

| | | |
|---|---|---|
| Item 18 | 1 | 1 |
| Item 19 | 1 | 1 |
| Item 20 | 1 | 1 |
| Item 21 | 1 | 1 |
| | | |
| *Domain 6. Editorial Independence* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 22 | 1 | 1 |
| Item 23 | 1 | 1 |
| | | |
| *Overall Assessment* | | |
| | Appraiser 2 | Appraiser 1 |
| OA1 | 1 | 2 |

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# A critical group appraisal of: MoH (Singapore) 2012. Depression using the AGREE II Instrument

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URL of this appraisal: http://www.agreetrust.org/group-appraisal/14584

Guideline URL:

| Domain 1 | Domain 2 | Domain 3 | Domain 4 | Domain 5 | Domain 6 | OA 1 | OA 2 |
|---|---|---|---|---|---|---|---|
| 50% | 56% | 18% | 25% | 4% | 0% | 8% | Yes - 0, Yes with modifications - 0, No - 2 |

| *Domain 1. Scope and Purpose* | | |
|---|---|---|
| | Appraiser 2 | Appraiser 1 |
| Item 1 | 3 | 4 |
| Item 2 | 4 | 5 |
| Item 3 | 3 | 5 |
| | | |
| *Domain 2. Stakeholder Involvement* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 4 | 6 | 5 |
| Item 5 | 3 | 2 |
| Item 6 | 5 | 5 |
| | | |
| *Domain 3. Rigour of Development* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 7 | 1 | 1 |
| Item 8 | 1 | 1 |
| Item 9 | 2 | 2 |
| Item 10 | 1 | 2 |
| Item 11 | 2 | 2 |
| Item 12 | 3 | 5 |
| Item 13 | 1 | 2 |
| Item 14 | 3 | 4 |
| | | |
| *Domain 4. Clarity of Presentation* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 15 | 2 | 3 |
| Item 16 | 2 | 1 |
| Item 17 | 3 | 4 |
| | | |
| *Domain 5. Applicability* | | |
| | Appraiser 2 | Appraiser 1 |

| | | |
|---|---|---|
| Item 18 | 1 | 2 |
| Item 19 | 1 | 2 |
| Item 20 | 1 | 1 |
| Item 21 | 1 | 1 |
| | | |
| *Domain 6. Editorial Independence* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 22 | 1 | 1 |
| Item 23 | 1 | 1 |
| | | |
| *Overall Assessment* | | |
| | Appraiser 2 | Appraiser 1 |
| OA1 | 1 | 2 |

Created online at www.agreetrust.org 10 June 2021

# A critical group appraisal of: NICE 2009. Depression in adults - recognition and management using the AGREE II Instrument

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URL of this appraisal: http://www.agreetrust.org/group-appraisal/14581

Guideline URL:

| Domain 1 | Domain 2 | Domain 3 | Domain 4 | Domain 5 | Domain 6 | OA 1 | OA 2 |
|---|---|---|---|---|---|---|---|
| 83% | 83% | 43% | 33% | 21% | 54% | 33% | Yes - 0, Yes with modifications - 0, No - 2 |

| *Domain 1. Scope and Purpose* | | |
|---|---|---|
| | Appraiser 2 | Appraiser 1 |
| Item 1 | 7 | 6 |
| Item 2 | 5 | 6 |
| Item 3 | 6 | 6 |
| | | |
| *Domain 2. Stakeholder Involvement* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 4 | 6 | 6 |
| Item 5 | 6 | 6 |
| Item 6 | 6 | 6 |
| | | |
| *Domain 3. Rigour of Development* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 7 | 6 | 5 |
| Item 8 | 6 | 5 |
| Item 9 | 2 | 3 |
| Item 10 | 2 | 2 |
| Item 11 | 2 | 3 |
| Item 12 | 2 | 2 |
| Item 13 | 6 | 6 |
| Item 14 | 3 | 2 |
| | | |
| *Domain 4. Clarity of Presentation* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 15 | 3 | 3 |
| Item 16 | 3 | 3 |
| Item 17 | 3 | 3 |
| | | |
| *Domain 5. Applicability* | | |
| | Appraiser 2 | Appraiser 1 |

| | | |
|---|---|---|
| Item 18 | 2 | 2 |
| Item 19 | 4 | 2 |
| Item 20 | 2 | 2 |
| Item 21 | 2 | 2 |
| | | |
| *Domain 6. Editorial Independence* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 22 | 2 | 3 |
| Item 23 | 6 | 6 |
| | | |
| *Overall Assessment* | | |
| | Appraiser 2 | Appraiser 1 |
| OA1 | 3 | 3 |

Created online at www.agreetrust.org 10 June 2021

# A critical group appraisal of: SIGN + HIS 2012. Management of perinatal mood disorders using the AGREE II Instrument

Created with the AGREE II Online Guideline Appraisal Tool.

No endorsement of the content of this document by the AGREE Research Trust should be implied.

Co-ordinator: Anders Sørensen

Date: 10 June 2021

Email: hello@psykologanders.dk

URL of this appraisal: http://www.agreetrust.org/group-appraisal/14570

Guideline URL:

| Domain 1 | Domain 2 | Domain 3 | Domain 4 | Domain 5 | Domain 6 | OA 1 | OA 2 |
|---|---|---|---|---|---|---|---|
| 75% | 50% | 27% | 22% | 0% | 4% | 8% | Yes - 0, Yes with modifications - 0, No - 2 |

| *Domain 1. Scope and Purpose* | | |
|---|---|---|
| | Appraiser 2 | Appraiser 1 |
| Item 1 | 6 | 5 |
| Item 2 | 6 | 5 |
| Item 3 | 6 | 5 |
| | | |
| *Domain 2. Stakeholder Involvement* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 4 | 3 | 5 |
| Item 5 | 1 | 2 |
| Item 6 | 7 | 6 |
| | | |
| *Domain 3. Rigour of Development* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 7 | 4 | 6 |
| Item 8 | 1 | 1 |
| Item 9 | 1 | 1 |
| Item 10 | 1 | 1 |
| Item 11 | 1 | 1 |
| Item 12 | 1 | 1 |
| Item 13 | 5 | 6 |
| Item 14 | 6 | 5 |
| | | |
| *Domain 4. Clarity of Presentation* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 15 | 2 | 3 |
| Item 16 | 1 | 2 |
| Item 17 | 3 | 3 |
| | | |
| *Domain 5. Applicability* | | |
| | Appraiser 2 | Appraiser 1 |

| | | |
|---|---|---|
| Item 18 | 1 | 1 |
| Item 19 | 1 | 1 |
| Item 20 | 1 | 1 |
| Item 21 | 1 | 1 |
| | | |
| *Domain 6. Editorial Independence* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 22 | 1 | 2 |
| Item 23 | 1 | 1 |
| | | |
| *Overall Assessment* | | |
| | Appraiser 2 | Appraiser 1 |
| OA1 | 1 | 2 |

Created online at www.agreetrust.org 10 June 2021


AGREE II

# A critical group appraisal of: NICE 2019. Depression in children and young people - identification and management using the AGREE II Instrument

Created with the AGREE II Online Guideline Appraisal Tool.

No endorsement of the content of this document by the AGREE Research Trust should be implied.

Co-ordinator: Anders Sørensen

Email: hello@psykologanders.dk

Date: 10 June 2021

URL of this appraisal: http://www.agreetrust.org/group-appraisal/14578

Guideline URL:

| Domain 1 | Domain 2 | Domain 3 | Domain 4 | Domain 5 | Domain 6 | OA 1 | OA 2 |
|---|---|---|---|---|---|---|---|
| 92% | 78% | 41% | 17% | 13% | 42% | 25% | Yes - 0, Yes with modifications - 0, No - 2 |

| *Domain 1. Scope and Purpose* | | |
|---|---|---|
| | Appraiser 2 | Appraiser 1 |
| Item 1 | 7 | 6 |
| Item 2 | 7 | 6 |
| Item 3 | 7 | 6 |
| | | |
| *Domain 2. Stakeholder Involvement* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 4 | 6 | 6 |
| Item 5 | 5 | 5 |
| Item 6 | 6 | 6 |
| | | |
| *Domain 3. Rigour of Development* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 7 | 7 | 6 |
| Item 8 | 7 | 6 |
| Item 9 | 2 | 3 |
| Item 10 | 2 | 2 |
| Item 11 | 2 | 2 |
| Item 12 | 1 | 2 |
| Item 13 | 6 | 4 |
| Item 14 | 1 | 2 |
| | | |
| *Domain 4. Clarity of Presentation* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 15 | 2 | 3 |
| Item 16 | 1 | 2 |
| Item 17 | 1 | 3 |
| | | |
| *Domain 5. Applicability* | | |
| | Appraiser 2 | Appraiser 1 |

| | | |
|---|---|---|
| Item 18 | 2 | 2 |
| Item 19 | 2 | 2 |
| Item 20 | 1 | 2 |
| Item 21 | 1 | 2 |
| | | |
| *Domain 6. Editorial Independence* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 22 | 3 | 4 |
| Item 23 | 3 | 4 |
| | | |
| *Overall Assessment* | | |
| | Appraiser 2 | Appraiser 1 |
| OA1 | 2 | 3 |

Created online at www.agreetrust.org 10 June 2021

# A critical group appraisal of: CANMAT 2016. Canadian network for mood and anxiety treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: Section 3. Pharmacological Treatments using the AGREE II Instrument

Created with the AGREE II Online Guideline Appraisal Tool.

No endorsement of the content of this document by the AGREE Research Trust should be implied.

Co-ordinator: Anders Sørensen

Date: 10 June 2021

Email: hello@psykologanders.dk

URL of this appraisal: http://www.agreetrust.org/group-appraisal/14567

Guideline URL:

| Domain 1 | Domain 2 | Domain 3 | Domain 4 | Domain 5 | Domain 6 | OA 1 | OA 2 |
|---|---|---|---|---|---|---|---|
| 50% | 28% | 25% | 19% | 6% | 50% | 8% | Yes - 0, Yes with modifications - 0, No - 2 |

| *Domain 1. Scope and Purpose* | | |
|---|---|---|
| | Appraiser 2 | Appraiser 1 |
| Item 1 | 4 | 4 |
| Item 2 | 3 | 4 |
| Item 3 | 5 | 4 |
| | | |
| *Domain 2. Stakeholder Involvement* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 4 | 2 | 2 |
| Item 5 | 1 | 1 |
| Item 6 | 5 | 5 |
| | | |
| *Domain 3. Rigour of Development* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 7 | 4 | 4 |
| Item 8 | 2 | 2 |
| Item 9 | 2 | 3 |
| Item 10 | 3 | 5 |
| Item 11 | 2 | 3 |
| Item 12 | 2 | 3 |
| Item 13 | 2 | 1 |
| Item 14 | 1 | 1 |
| | | |
| *Domain 4. Clarity of Presentation* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 15 | 2 | 3 |
| Item 16 | 2 | 2 |
| Item 17 | 2 | 2 |
| | | |
| *Domain 5. Applicability* | | |
| | Appraiser 2 | Appraiser 1 |

| | | |
|---|---|---|
| Item 18 | 1 | 2 |
| Item 19 | 1 | 2 |
| Item 20 | 1 | 2 |
| Item 21 | 1 | 1 |
| | | |
| *Domain 6. Editorial Independence* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 22 | 3 | 3 |
| Item 23 | 5 | 5 |
| | | |
| *Overall Assessment* | | |
| | Appraiser 2 | Appraiser 1 |
| OA1 | 1 | 2 |

Created online at www.agreetrust.org 10 June 2021


AGREE II

# A critical group appraisal of: WHO 2015 + 2016. mhGAP Intervention Guide for mental, neurological and substance use disorders in non-specialized health settings (2016) - WHO mGAP Guideline Update (2015) using the AGREE II Instrument

Created with the AGREE II Online Guideline Appraisal Tool.

No endorsement of the content of this document by the AGREE Research Trust should be implied.

Co-ordinator: Anders Sørensen

Date: 10 June 2021

Email: hello@psykologanders.dk

URL of this appraisal: http://www.agreetrust.org/group-appraisal/14572

Guideline URL:

| Domain 1 | Domain 2 | Domain 3 | Domain 4 | Domain 5 | Domain 6 | OA 1 | OA 2 |
|---|---|---|---|---|---|---|---|
| 94% | 69% | 43% | 11% | 27% | 58% | 17% | Yes - 0, Yes with modifications - 0, No - 2 |

| *Domain 1. Scope and Purpose* | | |
|---|---|---|
| | Appraiser 2 | Appraiser 1 |
| Item 1 | 7 | 7 |
| Item 2 | 7 | 6 |
| Item 3 | 7 | 6 |
| | | |
| *Domain 2. Stakeholder Involvement* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 4 | 5 | 6 |
| Item 5 | 4 | 3 |
| Item 6 | 7 | 6 |
| | | |
| *Domain 3. Rigour of Development* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 7 | 4 | 6 |
| Item 8 | 6 | 5 |
| Item 9 | 2 | 2 |
| Item 10 | 6 | 6 |
| Item 11 | 1 | 2 |
| Item 12 | 1 | 2 |
| Item 13 | 5 | 7 |
| Item 14 | 1 | 1 |
| | | |
| *Domain 4. Clarity of Presentation* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 15 | 1 | 2 |
| Item 16 | 1 | 1 |
| Item 17 | 2 | 3 |
| | | |
| *Domain 5. Applicability* | | |
| | Appraiser 2 | Appraiser 1 |

| | | |
|---|---|---|
| Item 18 | 2 | 2 |
| Item 19 | 6 | 5 |
| Item 20 | 2 | 1 |
| Item 21 | 1 | 2 |
| | | |
| *Domain 6. Editorial Independence* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 22 | 2 | 2 |
| Item 23 | 7 | 7 |
| | | |
| *Overall Assessment* | | |
| | Appraiser 2 | Appraiser 1 |
| OA1 | 2 | 2 |

Created online at www.agreetrust.org 10 June 2021


AGREE II

# A critical group appraisal of: NZGG + MoH 2008. Identification of Common Mental Disorders and Managemente of Depression in Primary Care using the AGREE II Instrument

Created with the AGREE II Online Guideline Appraisal Tool.

No endorsement of the content of this document by the AGREE Research Trust should be implied.

Co-ordinator: Anders Sørensen

Date: 10 June 2021

Email: hello@psykologanders.dk

URL of this appraisal: http://www.agreetrust.org/group-appraisal/14576

Guideline URL:

| Domain 1 | Domain 2 | Domain 3 | Domain 4 | Domain 5 | Domain 6 | OA 1 | OA 2 |
|---|---|---|---|---|---|---|---|
| 78% | 47% | 24% | 25% | 17% | 71% | 25% | Yes - 0, Yes with modifications - 0, No - 2 |

| *Domain 1. Scope and Purpose* | | |
|---|---|---|
| | Appraiser 1 | Appraiser 2 |
| Item 1 | 5 | 6 |
| Item 2 | 6 | 7 |
| Item 3 | 4 | 6 |
| | | |
| *Domain 2. Stakeholder Involvement* | | |
| | Appraiser 1 | Appraiser 2 |
| Item 4 | 5 | 6 |
| Item 5 | 1 | 1 |
| Item 6 | 5 | 5 |
| | | |
| *Domain 3. Rigour of Development* | | |
| | Appraiser 1 | Appraiser 2 |
| Item 7 | 4 | 3 |
| Item 8 | 2 | 2 |
| Item 9 | 2 | 2 |
| Item 10 | 2 | 2 |
| Item 11 | 4 | 2 |
| Item 12 | 2 | 1 |
| Item 13 | 4 | 3 |
| Item 14 | 3 | 1 |
| | | |
| *Domain 4. Clarity of Presentation* | | |
| | Appraiser 1 | Appraiser 2 |
| Item 15 | 3 | 2 |
| Item 16 | 2 | 2 |
| Item 17 | 3 | 3 |
| | | |
| *Domain 5. Applicability* | | |
| | Appraiser 1 | Appraiser 2 |

| | | |
|---|---|---|
| Item 18 | 2 | 2 |
| Item 19 | 3 | 2 |
| Item 20 | 2 | 2 |
| Item 21 | 2 | 1 |
| | | |
| *Domain 6. Editorial Independence* | | |
| | Appraiser 1 | Appraiser 2 |
| Item 22 | 6 | 7 |
| Item 23 | 4 | 4 |
| | | |
| *Overall Assessment* | | |
| | Appraiser 1 | Appraiser 2 |
| OA1 | 3 | 2 |

Created online at www.agreetrust.org 10 June 2021

# A critical group appraisal of: RANZCP 2020. The 2020 Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders using the AGREE II Instrument

Created with the AGREE II Online Guideline Appraisal Tool.

No endorsement of the content of this document by the AGREE Research Trust should be implied.

Co-ordinator: Anders Sørensen

Email: hello@psykologanders.dk

Date: 10 June 2021

URL of this appraisal: http://www.agreetrust.org/group-appraisal/14565

Guideline URL:

| Domain 1 | Domain 2 | Domain 3 | Domain 4 | Domain 5 | Domain 6 | OA 1 | OA 2 |
|---|---|---|---|---|---|---|---|
| 39% | 39% | 18% | 39% | 0% | 42% | 25% | Yes - 0, Yes with modifications - 0, No - 2 |

| *Domain 1. Scope and Purpose* | | |
|---|---|---|
| | Appraiser 1 | Appraiser 2 |
| Item 1 | 6 | 4 |
| Item 2 | 2 | 2 |
| Item 3 | 3 | 3 |
| | | |
| *Domain 2. Stakeholder Involvement* | | |
| | Appraiser 1 | Appraiser 2 |
| Item 4 | 3 | 3 |
| Item 5 | 2 | 1 |
| Item 6 | 6 | 5 |
| | | |
| *Domain 3. Rigour of Development* | | |
| | Appraiser 1 | Appraiser 2 |
| Item 7 | 2 | 2 |
| Item 8 | 2 | 1 |
| Item 9 | 2 | 1 |
| Item 10 | 2 | 2 |
| Item 11 | 3 | 2 |
| Item 12 | 4 | 2 |
| Item 13 | 3 | 3 |
| Item 14 | 1 | 1 |
| | | |
| *Domain 4. Clarity of Presentation* | | |
| | Appraiser 1 | Appraiser 2 |
| Item 15 | 4 | 3 |
| Item 16 | 3 | 3 |
| Item 17 | 3 | 4 |
| | | |
| *Domain 5. Applicability* | | |
| | Appraiser 1 | Appraiser 2 |

| | | |
|---|---|---|
| Item 18 | 1 | 1 |
| Item 19 | 1 | 1 |
| Item 20 | 1 | 1 |
| Item 21 | 1 | 1 |
| | | |
| *Domain 6. Editorial Independence* | | |
| | Appraiser 1 | Appraiser 2 |
| Item 22 | 3 | 3 |
| Item 23 | 4 | 4 |
| | | |
| *Overall Assessment* | | |
| | Appraiser 1 | Appraiser 2 |
| OA1 | 3 | 2 |

Created online at www.agreetrust.org 10 June 2021

# A critical group appraisal of: RCPSYCH 2003. Guideline for the management of late-life depression in primary care. using the AGREE II Instrument

Created with the AGREE II Online Guideline Appraisal Tool.

No endorsement of the content of this document by the AGREE Research Trust should be implied.

Co-ordinator: Anders Sørensen

Email: hello@psykologanders.dk

Date: 10 June 2021

URL of this appraisal: http://www.agreetrust.org/group-appraisal/14583

Guideline URL:

| Domain 1 | Domain 2 | Domain 3 | Domain 4 | Domain 5 | Domain 6 | OA 1 | OA 2 |
|---|---|---|---|---|---|---|---|
| 33% | 3% | 30% | 14% | 0% | 17% | 8% | Yes - 0, Yes with modifications - 0, No - 2 |

| *Domain 1. Scope and Purpose* | | |
|---|---|---|
| | Appraiser 2 | Appraiser 1 |
| Item 1 | 4 | 3 |
| Item 2 | 4 | 4 |
| Item 3 | 2 | 1 |
| | | |
| *Domain 2. Stakeholder Involvement* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 4 | 1 | 1 |
| Item 5 | 1 | 1 |
| Item 6 | 2 | 1 |
| | | |
| *Domain 3. Rigour of Development* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 7 | 6 | 6 |
| Item 8 | 6 | 6 |
| Item 9 | 2 | 1 |
| Item 10 | 2 | 4 |
| Item 11 | 1 | 1 |
| Item 12 | 2 | 4 |
| Item 13 | 1 | 1 |
| Item 14 | 1 | 1 |
| | | |
| *Domain 4. Clarity of Presentation* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 15 | 2 | 2 |
| Item 16 | 1 | 1 |
| Item 17 | 3 | 2 |
| | | |
| *Domain 5. Applicability* | | |
| | Appraiser 2 | Appraiser 1 |

| | | |
|---|---|---|
| Item 18 | 1 | 1 |
| Item 19 | 1 | 1 |
| Item 20 | 1 | 1 |
| Item 21 | 1 | 1 |
| | | |
| *Domain 6. Editorial Independence* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 22 | 1 | 1 |
| Item 23 | 3 | 3 |
| | | |
| *Overall Assessment* | | |
| | Appraiser 2 | Appraiser 1 |
| OA1 | 1 | 2 |

Created online at www.agreetrust.org 10 June 2021

# A critical group appraisal of: VA/DoD 2016. VA/DoD Clinical practice guideline for the management of major depressive disorder using the AGREE II Instrument

Created with the AGREE II Online Guideline Appraisal Tool.

No endorsement of the content of this document by the AGREE Research Trust should be implied.

Co-ordinator: Anders Sørensen

Email: hello@psykologanders.dk

Date: 10 June 2021

URL of this appraisal: http://www.agreetrust.org/group-appraisal/14571

Guideline URL:

| Domain 1 | Domain 2 | Domain 3 | Domain 4 | Domain 5 | Domain 6 | OA 1 | OA 2 |
|---|---|---|---|---|---|---|---|
| 78% | 61% | 50% | 17% | 8% | 8% | 17% | Yes - 0, Yes with modifications - 0, No - 2 |

| *Domain 1. Scope and Purpose* | | |
|---|---|---|
| | Appraiser 2 | Appraiser 1 |
| Item 1 | 5 | 6 |
| Item 2 | 5 | 5 |
| Item 3 | 7 | 6 |
| | | |
| *Domain 2. Stakeholder Involvement* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 4 | 6 | 6 |
| Item 5 | 1 | 2 |
| Item 6 | 7 | 6 |
| | | |
| *Domain 3. Rigour of Development* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 7 | 7 | 7 |
| Item 8 | 7 | 6 |
| Item 9 | 2 | 2 |
| Item 10 | 3 | 4 |
| Item 11 | 2 | 3 |
| Item 12 | 3 | 3 |
| Item 13 | 5 | 6 |
| Item 14 | 1 | 3 |
| | | |
| *Domain 4. Clarity of Presentation* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 15 | 2 | 3 |
| Item 16 | 1 | 2 |
| Item 17 | 2 | 2 |
| | | |
| *Domain 5. Applicability* | | |
| | Appraiser 2 | Appraiser 1 |

| | | |
|---|---|---|
| Item 18 | 1 | 2 |
| Item 19 | 2 | 2 |
| Item 20 | 1 | 2 |
| Item 21 | 1 | 1 |
| | | |
| *Domain 6. Editorial Independence* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 22 | 1 | 1 |
| Item 23 | 3 | 1 |
| | | |
| *Overall Assessment* | | |
| | Appraiser 2 | Appraiser 1 |
| OA1 | 1 | 3 |

Created online at www.agreetrust.org 10 June 2021

# A critical group appraisal of: WFSBP 2007. Guidelines for Biological Treatment of Unipolar Depressive Disorders in Primary Care using the AGREE II Instrument

Created with the AGREE II Online Guideline Appraisal Tool.

No endorsement of the content of this document by the AGREE Research Trust should be implied.

Co-ordinator: Anders Sørensen

Date: 10 June 2021

Email: hello@psykologanders.dk

URL of this appraisal: http://www.agreetrust.org/group-appraisal/14579

Guideline URL:

| Domain 1 | Domain 2 | Domain 3 | Domain 4 | Domain 5 | Domain 6 | OA 1 | OA 2 |
|---|---|---|---|---|---|---|---|
| 58% | 19% | 22% | 19% | 4% | 25% | 17% | Yes - 0, Yes with modifications - 0, No - 2 |

| *Domain 1. Scope and Purpose* | | |
|---|---|---|
| | Appraiser 2 | Appraiser 1 |
| Item 1 | 4 | 4 |
| Item 2 | 5 | 4 |
| Item 3 | 6 | 4 |
| | | |
| *Domain 2. Stakeholder Involvement* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 4 | 1 | 1 |
| Item 5 | 1 | 1 |
| Item 6 | 5 | 4 |
| | | |
| *Domain 3. Rigour of Development* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 7 | 2 | 3 |
| Item 8 | 1 | 3 |
| Item 9 | 1 | 3 |
| Item 10 | 1 | 2 |
| Item 11 | 2 | 3 |
| Item 12 | 1 | 3 |
| Item 13 | 1 | 2 |
| Item 14 | 4 | 5 |
| | | |
| *Domain 4. Clarity of Presentation* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 15 | 2 | 3 |
| Item 16 | 1 | 3 |
| Item 17 | 2 | 2 |
| | | |
| *Domain 5. Applicability* | | |
| | Appraiser 2 | Appraiser 1 |

| | | |
|---|---|---|
| Item 18 | 1 | 1 |
| Item 19 | 1 | 2 |
| Item 20 | 1 | 2 |
| Item 21 | 1 | 1 |
| | | |
| *Domain 6. Editorial Independence* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 22 | 4 | 4 |
| Item 23 | 1 | 1 |
| | | |
| *Overall Assessment* | | |
| | Appraiser 2 | Appraiser 1 |
| OA1 | 2 | 2 |

Created online at www.agreetrust.org 10 June 2021

# A critical group appraisal of: WFSBP 2013 + 2015. World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders, Part 1: Update 2013 on the acute and continuation treatment of unipolar depressive disorders + Part 2: using the AGREE II Instrument

Created with the AGREE II Online Guideline Appraisal Tool.

No endorsement of the content of this document by the AGREE Research Trust should be implied.

Co-ordinator: Anders Sørensen

Date: 10 June 2021

Email: hello@psykologanders.dk

URL of this appraisal: http://www.agreetrust.org/group-appraisal/14568

Guideline URL:

| Domain 1 | Domain 2 | Domain 3 | Domain 4 | Domain 5 | Domain 6 | OA 1 | OA 2 |
|---|---|---|---|---|---|---|---|
| 64% | 22% | 19% | 31% | 0% | 25% | 17% | Yes - 0, Yes with modifications - 0, No - 2 |

| *Domain 1. Scope and Purpose* | | |
|---|---|---|
| | Appraiser 2 | Appraiser 1 |
| Item 1 | 5 | 5 |
| Item 2 | 5 | 4 |
| Item 3 | 5 | 5 |
| | | |
| *Domain 2. Stakeholder Involvement* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 4 | 1 | 2 |
| Item 5 | 1 | 1 |
| Item 6 | 4 | 5 |
| | | |
| *Domain 3. Rigour of Development* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 7 | 2 | 2 |
| Item 8 | 1 | 1 |
| Item 9 | 3 | 3 |
| Item 10 | 2 | 2 |
| Item 11 | 2 | 2 |
| Item 12 | 1 | 2 |
| Item 13 | 1 | 1 |
| Item 14 | 4 | 5 |
| | | |
| *Domain 4. Clarity of Presentation* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 15 | 3 | 3 |
| Item 16 | 2 | 2 |
| Item 17 | 3 | 4 |
| | | |
| *Domain 5. Applicability* | | |
| | Appraiser 2 | Appraiser 1 |

| | | |
|---|---|---|
| Item 18 | 1 | 1 |
| Item 19 | 1 | 1 |
| Item 20 | 1 | 1 |
| Item 21 | 1 | 1 |
| | | |
| *Domain 6. Editorial Independence* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 22 | 2 | 4 |
| Item 23 | 2 | 2 |
| | | |
| *Overall Assessment* | | |
| | Appraiser 2 | Appraiser 1 |
| OA1 | 2 | 2 |

Created online at www.agreetrust.org 10 June 2021

# A critical group appraisal of: AACAP 2007. Practice parameter for the assessment and treatment of children and adolescents with depressive disorders. using the AGREE II Instrument

Created with the AGREE II Online Guideline Appraisal Tool.

No endorsement of the content of this document by the AGREE Research Trust should be implied.

Co-ordinator: Anders Sørensen

Date: 10 June 2021

Email: hello@psykologanders.dk

URL of this appraisal: http://www.agreetrust.org/group-appraisal/14580

Guideline URL:

| Domain 1 | Domain 2 | Domain 3 | Domain 4 | Domain 5 | Domain 6 | OA 1 | OA 2 |
|---|---|---|---|---|---|---|---|
| 53% | 14% | 27% | 19% | 0% | 13% | 17% | Yes - 0, Yes with modifications - 0, No - 2 |

| *Domain 1. Scope and Purpose* | | |
|---|---|---|
| | Appraiser 2 | Appraiser 1 |
| Item 1 | 5 | 5 |
| Item 2 | 4 | 3 |
| Item 3 | 4 | 4 |
| | | |
| *Domain 2. Stakeholder Involvement* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 4 | 2 | 3 |
| Item 5 | 1 | 2 |
| Item 6 | 2 | 1 |
| | | |
| *Domain 3. Rigour of Development* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 7 | 6 | 5 |
| Item 8 | 2 | 3 |
| Item 9 | 2 | 2 |
| Item 10 | 2 | 1 |
| Item 11 | 2 | 2 |
| Item 12 | 2 | 3 |
| Item 13 | 3 | 5 |
| Item 14 | 1 | 1 |
| | | |
| *Domain 4. Clarity of Presentation* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 15 | 2 | 2 |
| Item 16 | 2 | 2 |
| Item 17 | 3 | 2 |
| | | |
| *Domain 5. Applicability* | | |
| | Appraiser 2 | Appraiser 1 |

| | | |
|---|---|---|
| Item 18 | 1 | 1 |
| Item 19 | 1 | 1 |
| Item 20 | 1 | 1 |
| Item 21 | 1 | 1 |
| | | |
| *Domain 6. Editorial Independence* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 22 | 1 | 1 |
| Item 23 | 2 | 3 |
| | | |
| *Overall Assessment* | | |
| | Appraiser 2 | Appraiser 1 |
| OA1 | 2 | 2 |

Created online at www.agreetrust.org 10 June 2021


AGREE II

# A critical group appraisal of: AAP 2018. Guidelines for adolescent depression in primary care (GLAD-PC)]: Part I. Practice preparation, identification, assessment, and initial management + part II. Treatment and ongoing management using the AGREE II Instrument

Created with the AGREE II Online Guideline Appraisal Tool.

No endorsement of the content of this document by the AGREE Research Trust should be implied.

Co-ordinator: Anders Sørensen

Date: 10 June 2021

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URL of this appraisal: http://www.agreetrust.org/group-appraisal/14569

Guideline URL:

| Domain 1 | Domain 2 | Domain 3 | Domain 4 | Domain 5 | Domain 6 | OA 1 | OA 2 |
|---|---|---|---|---|---|---|---|
| 78% | 44% | 18% | 0% | 0% | 13% | 8% | Yes - 0, Yes with modifications - 0, No - 2 |

| *Domain 1. Scope and Purpose* | | |
|---|---|---|
| | Appraiser 2 | Appraiser 1 |
| Item 1 | 6 | 5 |
| Item 2 | 6 | 5 |
| Item 3 | 6 | 6 |
| | | |
| *Domain 2. Stakeholder Involvement* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 4 | 2 | 3 |
| Item 5 | 3 | 1 |
| Item 6 | 7 | 6 |
| | | |
| *Domain 3. Rigour of Development* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 7 | 4 | 4 |
| Item 8 | 2 | 3 |
| Item 9 | 2 | 2 |
| Item 10 | 2 | 3 |
| Item 11 | 2 | 2 |
| Item 12 | 1 | 1 |
| Item 13 | 1 | 2 |
| Item 14 | 1 | 1 |
| | | |
| *Domain 4. Clarity of Presentation* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 15 | 1 | 1 |
| Item 16 | 1 | 1 |
| Item 17 | 1 | 1 |
| | | |
| *Domain 5. Applicability* | | |
| | Appraiser 2 | Appraiser 1 |

| | | |
|---|---|---|
| Item 18 | 1 | 1 |
| Item 19 | 1 | 1 |
| Item 20 | 1 | 1 |
| Item 21 | 1 | 1 |
| | | |
| *Domain 6. Editorial Independence* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 22 | 1 | 1 |
| Item 23 | 2 | 3 |
| | | |
| *Overall Assessment* | | |
| | Appraiser 2 | Appraiser 1 |
| OA1 | 1 | 2 |

Created online at www.agreetrust.org 10 June 2021

# A critical group appraisal of: BPS + RCPSYCH + NCCMH + NICE 2010. Depression - The NICE guideline on the treatment and management of depression in adults - updated edition using the AGREE II Instrument

Created with the AGREE II Online Guideline Appraisal Tool.

No endorsement of the content of this document by the AGREE Research Trust should be implied.

Co-ordinator: Anders Sørensen

Date: 10 June 2021

Email: hello@psykologanders.dk

URL of this appraisal: http://www.agreetrust.org/group-appraisal/14585

Guideline URL:

| Domain 1 | Domain 2 | Domain 3 | Domain 4 | Domain 5 | Domain 6 | OA 1 | OA 2 |
|---|---|---|---|---|---|---|---|
| 56% | 58% | 36% | 33% | 8% | 50% | 25% | Yes - 0, Yes with modifications - 0, No - 2 |

| *Domain 1. Scope and Purpose* | | |
|---|---|---|
| | Appraiser 2 | Appraiser 1 |
| Item 1 | 5 | 4 |
| Item 2 | 4 | 3 |
| Item 3 | 5 | 5 |
| | | |
| *Domain 2. Stakeholder Involvement* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 4 | 6 | 3 |
| Item 5 | 7 | 1 |
| Item 6 | 5 | 5 |
| | | |
| *Domain 3. Rigour of Development* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 7 | 7 | 2 |
| Item 8 | 6 | 1 |
| Item 9 | 3 | 2 |
| Item 10 | 6 | 2 |
| Item 11 | 3 | 2 |
| Item 12 | 3 | 4 |
| Item 13 | 6 | 1 |
| Item 14 | 2 | 1 |
| | | |
| *Domain 4. Clarity of Presentation* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 15 | 3 | 2 |
| Item 16 | 3 | 2 |
| Item 17 | 4 | 4 |
| | | |
| *Domain 5. Applicability* | | |
| | Appraiser 2 | Appraiser 1 |

| | | |
|---|---|---|
| Item 18 | 2 | 1 |
| Item 19 | 3 | 1 |
| Item 20 | 2 | 1 |
| Item 21 | 1 | 1 |
| | | |
| *Domain 6. Editorial Independence* | | |
| | Appraiser 2 | Appraiser 1 |
| Item 22 | 2 | 4 |
| Item 23 | 7 | 3 |
| | | |
| *Overall Assessment* | | |
| | Appraiser 2 | Appraiser 1 |
| OA1 | 3 | 2 |

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*Article 3*

# The psychology of psychiatric drug action – a narrative review of psychiatric drugs as emotion regulation strategies

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## Abstract

Traditional accounts of how psychiatric drugs work have focused almost exclusively on the medical model and the biological effects of the drugs, assuming that they have specific biological effects that act as specific disease-targeting treatments (e.g., antidepressants, antipsychotics, mood stabilizers, anxiolytics). However, the medical model of psychiatric drug action is challenged by several lines of evidence, warranting exploration and discussion of alternative models of drug action. We present a *drug-centred* model that suggests that psychiatric drugs affect psychopathology through their general psychoactive effects on mental activity of feeling, thinking, and behaviour; that is, as a means of emotion regulation. Different drugs are thus categorized by their psychoactive properties and the nature of the drug-induced state of mind they produce. In addition, drugs may have psychological or symbolic effects irrespective of the chemical substance itself but inherently tied to being diagnosed and taking a pill, as is evident from the clinically insignificant differences between antidepressants and placebo, for example. Based on this model of drug action, we explore how drugs impact on emotion regulation and how this relates to psychopathology and psychotherapy. The drugs' psychoactive effects, particularly their ability to dampen down emotions, sedate, reduce arousal, and generally slow mental activity, may provide symptomatic treatment and relief from emotional suffering, but risk reinforcing patients' metacognitive beliefs and emotional schemes of uncontrollability, durability, intolerance, and incomprehensibility, which appear to drive psychopathology. We thus argue that psychotherapy and psychopharmacology target psychopathology at different levels and in ways that may conflict with each other. Psychotherapy aims at helping patients discover the controllability of difficult thoughts and emotions, make sense of painful emotions, learn distress tolerance and acceptance, and take problem solving actions on primary emotions, whereas drug treatment operates within the set of problematic metacognitive beliefs and emotional schemes by adding another emotion regulation strategy. Therefore, the rationale for drug treatment according to a drug-centred model consists of symptom suppression, which fails to address, and may even

reinforce, the fundamental psychological mechanisms that drive psychopathology. To constitute adaptive emotion regulation, the drug should either replace a more maladaptive emotion regulation strategy otherwise used by the individual or allow long-term strategies to come into place while symptoms and emotional distress are temporarily suppressed. These considerations are also relevant for patients withdrawing from psychiatric drugs, which may also involve people learning how to manage previously suppressed emotions.

## Two models of psychiatric drug action

### The medical model: psychiatric drugs as disease-targeting treatments

The medical model of drug action, also referred to as the 'disease-centred' model, is where psychiatric drugs are believed to act by correcting an abnormal brain state or biochemical imbalance. This model assumes that the symptoms of psychopathology arise from disrupted or dysfunctional biological processes that drugs help to rectify, and thus that patients have some sort of deficiency or abnormality. This hypothesised abnormal state that drugs are thought to correct is commonly thought to involve neurotransmitters. Thus, depression is supposed to be caused by abnormally low serotonin or noradrenalin levels and antidepressants are thought to reduce depressive symptoms by restoring the availability or activity of these neurotransmitters. Schizophrenia or psychosis is postulated to be caused by over-activity of the dopamine system and antipsychotics are thought to work by producing a compensatory lowering of dopamine activity. Theories of the neurochemical causation of mental disorders have, in fact, often derived from the observed actions of drugs. The dopamine hypothesis of schizophrenia, for example, was constructed following observations that some early antipsychotics antagonised the actions of dopamine. Similarly, the serotonin theory of depression was popularised after serotonin-re-uptake blocking drugs started to be widely marketed. Thus, chemical imbalance theories of psychopathology arose from this

'backwards' reasoning, not from controlled research that indicated independent abnormalities in neurotransmitter systems, and evidence of such abnormalities continues to be lacking.[1–3]

In the case of serotonin and depression, although findings of serotonin abnormalities associated with depression have been proclaimed, they have not been consistently replicated and the effects of medication use have not been controlled for. A recent umbrella review found no evidence that levels of serotonin in plasma or the serotonin metabolite, 5HIAA in CSF are abnormal in depression, and no evidence of abnormalities of serotonin receptors, the serotonin transporter (SERT), or the SERT gene, including an interaction between the SERT gene and environmental adversity.[4] PET and SPECT studies find no correlation between SERT occupancy of antidepressants and clinical effect on depression[5–8] (yet may not have been powered to detect such correlations). Experiments intended to lower serotonin levels do not provoke depression in volunteers, and effects in patients are weak and inconsistent and likely explained by past or current medication use.[4] Links between noradrenaline and depression are equally inconsistent.[9] Finally, achieving a sustained elevation or inhibition of neurotransmission as an effect of continuous pharmacological intervention may not be possible, as neurotransmitter levels are under homeostatic control.[10]

Research on dopamine in schizophrenia has failed to show abnormalities of dopamine metabolites in urine or CSF, stimulant-induced psychosis has not, in fact, been linked to dopamine, and the increases in dopamine receptor number and affinity that have been observed may be attributable to the physiological adaptations to the use of dopamine-blocking drugs; that is antipsychotics.[3] Some recent experiments report increased L-dopa uptake in people with psychosis compared to controls[11] and increased dopamine release in response to amphetamine.[3] However, studies are inconsistent and the number of drug naïve patients in these studies is small overall. Moreover, none have controlled for the increased activity of dopamine that is known to be associated with stress, arousal, activity, hunger, and other states that may affect people with psychosis more than those without.[2,3]

In response to the lack of evidence confirming the principle neurotransmitter hypotheses of mental disorders, other biological mechanisms have been hypothesised, including abnormalities in neurotrophic factors (brain-derived neurotrophic factor),[12–14] neural circuitry,[15,16] acetylcholine,[17,18] glutamate,[19–23] cannabinoid receptors,[24–27] and mechanisms related to the physiological adaptations to the initial drug effects.[28] These all suffer from the same problems as the principle neurotransmitter hypotheses; correlative data with no evidence of causation and lack of replicable evidence. It is also not clear how drug effects would obviously correct such abnormalities, although some commentators have posited some theoretical mechanisms,[16,28] or whether pharmacological intervention is the only way of achieving neurological changes given the epigenetic and neuroplasticity principles of bidirectional causality between the genetic, neural, behavioural, and environmental levels.[29–31] Even though there is no consistent evidence for any biological abnormality in depression, even if there were, drugs would not be the only way to address it, since there is evidence that other interventions, including psychotherapy and placebo can produce neural changes.[32–34]

Other evidence also fails to support the medical model of drug action. Comparative studies fail to show that drugs that are thought to work by targeting the underlying biological basis of symptoms can be differentiated from drugs that have similar psychoactive effects but do not have the same biological action. Studies thus show that numerous psychoactive drugs that are not classified as antidepressants, for example, have effects that are comparable to antidepressants in people with depression, including antipsychotics,[35] barbiturates,[36] benzodiazepines,[37–39] stimulants,[40] opiates,[41] St. John's wort,[42] amylobarbitone, lithium, liothyronine, and adinazolam.[39] Moreover, a drug that inhibits serotonin activity by blocking serotonin receptors, tianeptine, has been found to exert 'antidepressant' effects and is marketed as an antidepressant in many countries; that is, despite having opposite pharmacodynamics of SSRIs.[43,44] In psychosis and schizophrenia, sedative drugs such as benzodiazepines appear to have effects similar to antipsychotics.[45,46] Moreover, some effective antipsychotics, such as clozapine, lack significant

dopamine-blocking activity.[47] Animal research also fails to identify that psychiatric drugs have disease or disorder-specific actions.[48]

Placebo-controlled trials do not confirm that psychiatric drugs have disease-targeting effects. Differences between antidepressants and placebo, for example, are small and likely clinically insignificant (Table 1)[39,49–66] and the trials are riddled with methodological shortcomings and high risk of bias[60] including inadequate blinding,[67,68] confounding withdrawal symptoms with relapse,[69,70] inappropriate washout of patients' previous medications resulting in preselection of patients most likely to respond,[71–73] publication bias and outcome selection bias,[74–77] and generally short follow-up. Consequently, the modestly different outcomes between patients on inert placebo vs. active antidepressants have several other possible explanations, including bias, than the active ingredients in the drug, and much larger differences would be expected if the active drug was driving the improvement. Reductions on subjective symptom rating scales may be a consequence of placebo effects, placebo effects amplified by the experience of adverse effects or the feeling of taking an active drug, or they may be directly due to the psychoactive or mind-altering effects of the drug as explained by an alternative 'drug-centred' model of drug action as presented below.

Despite the lack of supporting evidence, the medical or disease-centred model of drug action continues to be assumed to be the explanation for the observed and experienced effects of psychiatric drugs. It underpins the understanding of drug action set out in psychiatric and psychopharmacology textbooks[78–80] and forms the basis of the vast majority of research on psychiatric drugs.[48] Other explanations are rarely acknowledged, even though it cannot be denied that psychiatric drugs have mind-altering effects that occur independently of the presence of psychopathological symptoms and are bound to impact on those symptoms in one way or another when they are present.

**The drug-centred model: psychiatric drugs as psychoactive substances**

There is an alternative way of understanding how psychiatric drugs work, however, which is referred to as

the ‘drug-centred’ model of drug action. Psychiatric drugs are psychoactive substances that alter normal mental activity, that is, thinking, feeling, and behaviour. When someone who has a psychopathological disorder takes a psychoactive drug, these mental alterations are superimposed upon the underlying distress or disturbance. Being in the drug-induced state may be experienced as preferable to the underlying state by the individual concerned, or by others who are disturbed by the individual’s behaviour. Interestingly, at the advent of modern psychiatric drug treatment, a similar drug-centred approach appeared dominant,[48,81] as illustrated in the quotes in Box 1.

In a drug-centred model, psychiatric drugs are categorized by the nature or quality of the drug-induced state they produce upon consumption, rather than by their alleged specific actions on alleged biochemical abnormalities.[82] Psychiatric drugs produce a range of altered states (see table 2) with varying onset of action and degree of effect, and with individual variations. Most of them are sedative substances that reduce neurological activity and arousal (and much activity in the rest of the body) in one way or another. Some are stimulants, which increase arousal. Sedative effects reduce agitation and behavioural disturbance, and some psychiatric drugs such as benzodiazepines and antipsychotics are used for their ability to reduce arousal, agitation, and activity in some situations, such as the management of aggressive behaviour, rather than for any specific disease-targeting effect.[83] Stimulants are used to prolong wakefulness by pilots and to enhance focused attention in people with concentration difficulties. Psychiatric drugs also impact on emotions and thoughts, and these effects may be particularly relevant for people experiencing psychopathology.

Most commonly prescribed psychiatric drugs, and many recreational substances, whether sedative or stimulant, appear to share the property of reducing the intensity or subtlety of emotions. Although there are few qualitative studies into the subjective experience of taking psychiatric drugs, in some of the ones that exist, as well as other forums in which patients can express their experiences of prescribed medication, people generally describe drug-induced effects on emotions in the following terms:

apathy, emotional indifference, emotional detachment, relief from painful emotions, caring less for themselves and others, emotional blunting (a loss of emotions in general, both positive and negative), emotional diminution, a reduction in emotional sensitivity, a sense of numbing of the emotions, or a suppression or even absence of emotional life.[84–93]

It can be argued that all altered states produced by drugs make people less sensitive to complex features of the human environment, such as the reactions of other people, and less engaged with one's fundamental values and goals. Even drugs that increase arousal, such as stimulants, or the intensity of sensations such as psychedelics, tend to narrow the range of attention, inducing the individual to become focused on a certain set of stimuli and reducing their responsiveness to other aspects of the environment. Hence, as well as being less intense in many instances (though not all - some drugs like alcohol and benzodiazepines can famously induce strong emotional reactions), emotions experienced while under the influence of a psychoactive substance are cruder and less likely to reflect a person's underlying principles. The power of discrimination - of being able to evaluate a situation according to what one really values that is the key driver of natural emotional reactions - is diminished.

Psychiatric drugs can therefore both suppress the intensity of emotions and subtly alter their character. Depending on the individual and the situation, these emotional alterations produced by psychiatric drugs may or may not be perceived as helpful. The emotional suppression may be experienced as a relief from intense and overwhelming unpleasant emotions and the slowing of mental activity may reduce the frequency of unwanted ruminations, worries, traumas, or intrusive psychotic experiences. When this is the case, it means that the mental alterations produced by the drugs, that is, their psychoactive effects, are preferred to the symptomatic state.

From a psychological perspective, it can be argued that the mind-altering and psychoactive effects of psychiatric drugs qualify as emotion regulation, defined as 'the processes by which individuals influence which emotions they have, when they have them, and how they experience and express these

emotions'[94] or 'actions taken by a person to modify/change emotions or increase or reduce their intensity'.[95] Furthermore, psychiatric drug treatment and the associated process of medical assessment and diagnosis may also impact on emotions and recovery through the placebo effect and other non-pharmacological or psychological mechanisms of action; that is, effects related to the taking of a pill and the meaning and context around it rather than the chemical substance itself.

These effects are likely to be enhanced by the idea that drugs act in a disease-centred or medical manner. In other words, if people believe their problems are due to an underlying brain dysfunction and that drugs can help correct this, then they may find solace (at least short-term) in the idea that they have found a solution to their problems, and this may lessen their negative emotions.

Therefore, prescribed psychiatric drugs can modify negative emotional states through direct pharmacological (psychoactive) effects, placebo effects, or effects that inhere in the meaning and context of taking a prescribed medical drug rather than in the chemical substance itself.

How we regulate our emotions has been established as both an etiological and maintaining factor to psychopathology, transdiagnostically, and thus as a specific target for intervention.[96–101] The clinical question is whether – and when – emotion regulation by medication is an adaptive or maladaptive strategy, respectively.

## Psychopathology as an emotion regulation problem

### Emotions and psychopathology

Contemporary evidence-based psychological models of psychopathology[102–105] suggest an interplay between, in this causal order, 1) what we think and believe about our thoughts (metacognitive beliefs) and about our emotions (emotional schemes); 2) emotional episodes or other triggers occurring and their intensity; 3) emotion regulation strategies used to cope with unpleasant emotions; and 4) psychopathology

(Figure 1). Underlying beliefs about cognitions and emotions drive strategy choice, which in turn determines whether strong emotional episodes tend to develop into states of psychopathology or remain in their initial 'primary' state. This distinction between normal emotional suffering and psychopathology goes by many names; pure pain vs. dirty pain,[106] shallow depression vs. deep depression,[107] primary emotions vs. secondary emotions,[95,108] and having a problem 1 vs. a problem 2.[103] It is also reflected in the diagnostic manuals ICD-11[109] and DSM 5,[110] where a time criterion is used to delineate non-pathological suffering from pathology, e.g., if symptoms persist for a certain period of time, indicating that emotion regulation is impaired. Indeed, depressed subjects report that their negative affect lasts longer after aversive life events compared with non-clinical groups.[111,112]

Consider the following case. Negative affect arises in a person holding beliefs of incomprehensibility, uncontrollability, and durability. He believes that his emotion does not make sense, has no informative value, that he cannot control it, and that the distress will last indefinitely and escalate. As a result, he seeks out alcohol, distraction, and rumination as strategies aimed at numbing and avoiding the distress here and now. Securing external control helps him because he does not believe he has executive self-control or that this emotion, too, will pass. Furthermore, believing his emotions make no sense, are shameful, and unique to him, he conceals the emotional expression and does not seek out validation and connectedness. If he could come to associate his negative affect (e.g., sadness and loneliness) with his higher values of love and dedication and recognize it as a temporary reminder of someone he loved or is currently missing in life; if he could experience the distress rise and fall without overwhelming him and discover that he has, in fact, attentional control over it; and if he could realize that others experience similar feelings when in similar situations; then he might be less attracted to alcohol, distraction, ruminations, worries, and isolation as means of avoiding or suppressing his feelings.

Emotions are responses to self-relevant stimuli.[113] Negative affect in its primary form is a normal and valuable signal when we are off track from our values, goals, or needs. When thwarted or

unfulfilled, 'primary' unpleasant emotions like anxiety, low mood, or agitation are elicited. Just like hunger is designed to be unpleasant to motivate us to eat, unpleasant primary emotional states are not signs of pathology, but of a well-functioning and adaptive system that produces distress when there is something to be distressed about.

Mood disorders, as an example, is understood as the outcome of difficulties regulating emotions, where emotions are ruminated on, worried about, attempted suppressed, and avoided rather than accepted, felt, reappraised, defused from, and/or used as valuable information to problem-solve and indicate the status of one's psychological needs, goals, and values.[95,101,114]

**Emotion regulation strategies and psychopathology**

Emotion regulation strategies are traditionally classified as maladaptive or adaptive depending on their long-term effects and on what the person is trying to achieve.[94,95,101,115] Suppression, avoidance, substance use, rumination, and worry generally correlate positively with symptoms of psychopathology across diagnoses and are considered maladaptive, whereas acceptance, problem solving, cognitive reappraisal, and cognitive defusion are associated with lower levels of or no psychopathology and are considered adaptive.[101,116,117] In addition to choice of strategies, the maladaptive emotion regulation style appears to be context-insensitive and inflexible[118,119] and motivated by experiential avoidance, defined as 'the tendency towards avoiding any such unpleasant inner experiences as thoughts, emotions, feelings, sensations, memories and drives by trying to change or modify their content, form, frequency, intensity or impact even when useless or in explicit conflict with goals or values' or 'efforts to avoid or escape the experience and awareness of one's own emotions'.[120–124] The emotion regulation strategies considered maladaptive serve the function of experiential avoidance and short-term relief. However, in doing so and if used extensively, they risk backfiring long-term, extending the initial negative affect into what is conceptualized as a psychopathological state of depression, anxiety, psychosis, etc. (Figure 1).

Evidence that psychopathology is the result of maladaptive emotion regulation includes cross-sectional studies showing a positive correlation between various diagnoses and emotion regulation skills;[100,115,116,121,125–130] longitudinal studies showing a predictive value of emotion regulation on mental health;[122–124,131–134] mediational studies showing that emotion regulation skills mediate the relationship between stressors and development of psychopathology,[135,136] attachment and depression,[137] early life stress and PTSD, depression and anxiety,[138] childhood abuse/neglect and PTSD,[139] and self-compassion and recurrent depression;[140] and various experimental studies showing an association between maladaptive strategies and paradoxical increase in negative affect.[141–149] Furthermore, low distress tolerance is associated with anxiety disorders, mood disorders, PTSD, and borderline;[150–154] appraising emotions as unacceptable mediates the relationship between negative affect and use of suppression as a strategy;[155] and symptom severity and recovery following cognitive behavioural therapy is associated with acceptance and tolerance of negative affect.[96]

**Metacognitive beliefs and emotional schemes as the root cause of maladaptive emotion regulation**

The metacognitive model and the emotional schema model further suggest that emotion regulation strategies are driven by more fundamental beliefs which consist of what we think and believe about our thoughts (metacognitive beliefs)[102,103] and emotions (emotional schemes).[104,105] These beliefs get activated when a trigger enters our mind, be it a thought, an emotion, a traumatic memory, or a sensation, as part of the process of deciding how to cope (Figure 1). An important characteristic of these models is the distinction between the occurrence of triggers and what we do to cope with them; the fundamental control we have over mental content claimed in both models lies in the control over what to do with the triggers, not whether they occur or what their content is.

Metacognitions are cognitions about cognitions, e.g., my thoughts are uncontrollable, my thoughts will last forever, my thoughts are dangerous, I must follow and act on my thoughts, I should not

think certain thoughts, I cannot ignore my worrying thoughts, I cannot stop worrying. Emotional schemes are our beliefs and ideas about emotion, e.g., I cannot tolerate my painful emotions, my emotions are out of my control, my emotions are durable and will escalate, my emotions make no sense and are unique to me, I should not have these emotions, others will not understand how I feel, I should only feel one way about things, negative affect is something to get rid of and away from.

Holding beliefs of uncontrollability, durability, and incomprehensibility, for example, lead naturally to experiential avoidance and a sense of urgency to terminate the distress. This painful state compels us to resort to strategies like avoidance, suppression, substance use, binge eating, isolation, excessive distraction, inactivity, rumination, and worry that can work here and now but that risk backfiring long-term (Figure 1). For a person holding these beliefs, such emotional control strategies are attractive because they may provide rapid relief; they are solutions to the problems caused by believing that one's emotions and thoughts are out of control, overwhelming, durable, and make no sense. However, a paradox emerges in that overreliance on these strategies will confirm the problematic beliefs and thus maintain the idea of painful emotions and excessive thoughts as experientially intolerable, thus creating a psychopathological loop.[102,104] The solution becomes the problem, and one definition of psychopathology is when these dynamics conflict with the individual's long-term goals and values in addition to having no lasting effects on the initial negative affect.[117] Via experiential avoidance, however, acute and short-term relief may get priority over long-term solutions when the emotional distress is overwhelming.

The clinical question is where and how to intervene this cycle between beliefs, triggers, emotion regulation strategies, and the potentially resulting psychopathological states. Both the concepts of metacognitive beliefs and emotional schemes are consistently conceptualized as beliefs, implying that the different statements are something we can believe more or less in and in ways that are changeable. The psychological solution to psychopathology involves achieving meta-level change in the patient by targeting and modifying the underlying beliefs that drive the maladaptive emotion regulation style. This can resolve

psychopathology by diminishing the attractiveness of the maladaptive emotion regulation strategies that backfire and create the 'dirty pain'. The therapeutic aim is thus to move patients from a maladaptive to an adaptive emotion regulation style that serves his/her values and long-term goals rather than revolves around experiential avoidance. Ideally, what remains of sustained negative affect is unpleasant primary emotion when there is something to feel bad about, e.g., when a personal value, goal, or need is unmet or threatened.

For example, beliefs that emotions and thoughts are uncontrollable, intolerable, and will last indefinitely can be targeted in-session by deliberately unfolding a strong and unpleasant emotion or trauma and then guide the patient through the episode from a safe space while observing it rise and fall. That is, while discouraging attempts and inclinations to suppress or avoid the distress. Emotions and thoughts are episodic and temporary by nature, but our patients rarely get to the fall-part due to routinely terminating the distress acutely through various maladaptive strategies. While alleviating the distress, this prevents the patient from challenging his beliefs, which then remain unchanged, and from developing the alternative strategies that arise from a different set of beliefs. The therapist may use metacognitive techniques to help the patient direct attention alternately towards and away from the emotion, resulting in a corresponding increase and decrease in emotional intensity, respectively.[156] Experiencing that the strong and painful emotion did not escalate or last indefinitely, and that it was under some attentional control, challenges and potentially disconfirms the beliefs that emotions are uncontrollable, overwhelming, and will last indefinitely. Other techniques include targeting incomprehensibility by identifying the patient's unmet or threatened values, goals, or needs and linking that absence to the painful emotions; targeting uncontrollability via the attentional training technique and detached mindfulness;[103,157] and targeting guilt and shame via validation.[105] For more psychotherapeutic techniques, see the treatment manuals of metacognitive therapy[103] and emotional schema therapy.[105]

Evidence shows that psychotherapy outcomes are mediated by changes in emotion regulation, indicating that patients recover partly because they learn to regulate their emotions better.[96,134,158] This suggests that emotion regulation is a modifiable treatment target, that adaptive emotion regulation is a skill that can be acquired, and that maladaptive patterns are not inevitable or permanent. As explained above, the drug-centred model highlights the way that psychiatric drugs, like all psychoactive substances, change mental states, emotions, and behaviours. In the next section we discuss how psychiatric drugs may facilitate or impede the development of adaptive emotion regulation in patients, based on the metacognitive and emotional schema models as just presented.

## Psychiatric drugs, emotion regulation, and psychopathology

### Psychoactive effects and emotion regulation

By altering emotion, thought, and behaviour, psychopharmacology intervenes against the symptoms caused by holding problematic beliefs or the intensity of the initial triggering emotion, which naturally will present as a relief and symptom reduction. Drugs thus operate within the system of problematic beliefs by accepting them and accordingly adding another emotional control strategy aimed at downregulating symptoms and emotional distress; in contrast, psychotherapy operates outside the beliefs at the meta-level, trying to identify and challenge the problematic beliefs. Therapeutic drug effects include reduced arousal, inducing a state of calmness and relaxation, temporary emotional indifference from too painful emotions, and dampening of excessive thoughts by slowing overall mental activity. Fast acting and potent drugs like benzodiazepines and most neuroleptics may have therapeutic value in the acute phase by offering rapid relief from intense anxiety attacks, agitation, deep depressive episodes, sleep deprivation, or psychotic symptoms. The sedative effects of benzodiazepines may reduce the physiological fluctuations that trigger anxiety and panic attacks. However, high relapse rates can be expected when the drug is withdrawn, as the patient's cognitive level of catastrophizing when interpreting bodily signals was not

modified by the drug, which may further be exacerbated by physiological withdrawal effects. Antidepressants such as SSRIs appear to have only subtle emotion-numbing properties (but large placebo effects) and are therefore of little value in an acute crisis but may reduce the overall intensity of unpleasant emotions, including anxiety and depression, when taken continuously. Finally, any drug that dampens or creates distance from excessive *what if*-thoughts (worry) and *if just*-thoughts (rumination) central to mood and anxiety disorders (that is, in patients holding beliefs of uncontrollability and durability etc.) may provide relief from the emotional distress otherwise caused by following these often negative thought streams. However, such solution means that the underlying beliefs driving the extended thinking go unchallenged and unchanged.

The attractiveness of these drug-induced states depends on the patient's beliefs about uncontrollability, durability, incomprehensibility, guilt and shame, etc. However, while reducing symptoms and helping patients feel better, emotion regulation by medication risks confirming and reinforcing the patients' problematic beliefs (illustrated by the bidirectional arrows in Figure 1), thus constituting maladaptive emotion regulation. Put simply, in a symptom reduction- and feel better-agenda, it is possible to succeed in reducing symptoms while inadvertently reinforcing the beliefs and maladaptive emotion regulation style giving rise to the symptoms, suggesting a separation of these two levels in the emotion regulation model of psychopathology. Continuous emotion regulation by medication – being an external substance by definition – violates several psychological concepts related to recovery, e.g., agency, internal locus of control, empowerment, beliefs of controllability, acceptance, and self-executive control. Psychology and psychopharmacology thus appear to target psychopathology at different levels and in ways that may conflict with each other. Psychiatric drugs risk reinforcing the patients' passivity towards their emotions, lack of agency and controllability, experiential avoidance, beliefs of durability and escalation if painful emotions are not terminated here and now, the belief that emotions are not comprehensive, sense of urgency, and external locus of control. The implicit message conveyed when prescribing a pill – in both models of drug action – is that an external substance is necessary for improvement and that the individual's

own resources (whether actual or potential) are not enough. This message, whether implicitly or explicitly communicated, will likely reinforce beliefs that the problem is uncontrollable, overwhelming, and incomprehensible. The drug-centred model makes the emotion-modifying effects of drugs transparent, however, and therefore enables people to appreciate the potentially self-defeating effects of continuous use, and the need for developing other, more permanent and adaptive solutions.

No drug can selectively target 'abnormal' or unwanted emotions; drugs will also affect primary (functional) emotions which provide valuable information about personal values, goals, and needs. Blunting primary emotions with medication risks driving the person off track from his/her values, goals, and needs, thus creating more distress long-term, potentially of the existentialistic type. Nevertheless, cutting contact with unpleasant primary emotions will feel immediately emotionally attractive and present as symptom reduction on rating scales, but will be highly maladaptive. If lethargy, emotional indifference, and avoidance are attractive mental states, something is usual wrong in life, and then that is the problem to target with respect to long term recovery. In a drug-centred model, drug treatment does not reverse an underlying disorder, but therapeutic effects arise from the superimposition of the drug-induced state onto the symptomatic state. In doing so, it is crucial not to confuse experiential avoidance with genuine and lasting therapeutic change. Along with temporary emotional suppression at times of crises, pharmacological avoidance and suppression may be worthwhile if it is used to replace a more harmful strategy currently used by the patient, such as cutting, alcohol misuse, social isolation, excessive distraction, psychosis, or rituals – however that hierarchy is determined. Drugs might also be useful if they can introduce a temporary disruption to a rigid and inflexible behaviour pattern by introducing variation in thoughts, attention, behaviour, experiences, or emotions. Whether intervening in this way is adaptive or maladaptive depends on each individual's context and circumstances, and whether the overall symptomatic relief is used to allow other long-term strategies to come in place.

In essence, the aim of psychotherapy regarding emotion regulation is to help patients be able to feel *more* rather than feel *better*,[105] as the feel better-agenda risks misinterpreting maladaptive emotion regulation strategies like suppression and avoidance as improvement. Feeling more in the sense of accepting the nature of our emotions and understanding their meaning, and thus engage less in the maladaptive strategies that arise from experiential avoidance and that backfire long-term. If there is something to feel bad about, it is not improvement to feel better. Long-term goals are to build resilience and acceptance rather than reduce discomfort; to normalize and validate painful primary emotions rather than seek escape and avoidance; and to learn to apply detached mindfulness[103] or cognitive defusion[117] techniques to negative excessive thoughts rather than suppress them. To some extent, stand-alone long-term psychiatric drug treatment is incompatible with these goals.

**Non-pharmacological, psychological, and placebo effects of psychiatric drugs**

Psychiatric drug treatment is not a purely biochemical matter to be considered in isolation. In addition to the pharmacological effects (both direct biological and psychoactive), a non-pharmacological route of action is evident from the clinically insignificant difference between antidepressants and placebos, for example (Table 1). That antidepressants do not outperform placebos in terms of clinical (and often statistical) significance does not mean that taking and starting antidepressants cannot lead to improvement, but that such improvement may, in part, be attributable to non-pharmacological factors. Few efforts have been made to understand these non-pharmacological mechanisms, which could include the following:

First, patients may start sharing their feelings with peers and loved ones upon receiving an official diagnosis; it gets easier to talk about. In such case, 'starting drug treatment' was not the only variable that changed, but also going from suffering alone to sharing with loved ones. This change may in

itself be therapeutic through emotional validation, which is an emotional schema closely correlated with improvement of depression, suggesting that depression has significant interpersonal components.[105,159]

Second, the treatment rationale and explanation provided in the medical model may function to temporarily terminate and satisfy ruminations concerning "what's wrong with me? What should I do? How do I get out of this suffering?" and to counteract self-criticism. This may lead to emotional improvement - as rumination is a core transdiagnostic feature of psychopathology - to the extent that these so-called trigger thoughts[102] are subsequently engaged with to a lesser extent than before getting diagnosed. Unanswered and incomprehensible suffering makes us ruminate, potentially leading to depressive episodes or anxiety due to the long hours spent in a negative mode of mind which affects our emotions in the here and now. However, since rumination is a tendency and a general strategy driven by beliefs of uncontrollability and incomprehensibility among others, it is likely to return – possibly reinforced – if terminated via external means or by 'answering it', as that does not produce metalevel change. Relief caused by these mechanisms is often short-lived. Furthermore, two of the identified common factors of effective therapy across different therapeutic schools may be activated by the medical model: 1) providing an explanation for the symptoms that is accepted by and makes sense to the patient and 2) a corresponding ritual or set of principles for behaviour change.[160,161] All effective therapies, including psychiatric drug treatment, share these aspects, which may contribute to improvement regardless of the active drug.

Third, maybe a sense of hope and positive expectation was induced when initiating drug treatment, countering the hopelessness and negative mode of mind that characterize mood disorders. Such positive beliefs and expectations may be self-fulfilling through the placebo effect, to some degree, and occur regardless of the drug itself but are inherently tied to taking the pill and undergoing diagnosis. Placebo effects will likely be enhanced if a drug is presented as working in a disease-centred or medical manner as acting to reverse an underlying biological abnormality.

Although placebo effects are usually considered beneficial, and, like the psychoactive effects of drugs, they may indeed produce short-term relief from a deep depression or period of stress, they can also have negative consequences if they divert people from realizing other causes of their improvement. The symbolic meanings of drug treatment ('I have a disease; I need a medical cure') may distract people from appreciating both the positive effects of their own efforts and the fact that painful emotions do not last forever.

Drugs do blind for non-drug reasons for recovery. Patients who recovered while on drugs and continued taking them may live substantially different lives now compared with back when suffering was at its highest. Deliberately describing and comparing life now with back then usually reveals several other changes besides starting the drug, all of which may have contributed to recovery. In our clinical experience, this therapeutic exercise may reveal things like a substantial change of habits and routines away from unhealthy patterns that the mind and body previously informed about via unpleasant emotions; more structure and direction in life; or the passing of a crisis that was re-acted to. Any change identified may potentially have contributed to recovery, whether the drug was involved in making the change or not, but sometimes these non-drug variables get little credit and attention because recovery was immediately attributed to the drug. Therapeutic questions include what it meant for the person to start sharing, get an explanation, break isolation, change habits, etc., and whether it makes sense for him/her that the suffering centred around the matter identified. Exploring our patients' stories of recovery in this way may reveal other themes than the drug. Stories about personal victories and development, about making it through tough times and rising back up, about breaking isolation and bringing close-ones closer, about natural fluctuations of mood, of active things that people do to make positive changes in their lives etc. This potentially renders the drug irrelevant – and even harmful – to sustained recovery and thus feasible to withdraw, as they risk maintaining the idea of emotions as uncontrollable and overwhelming. The medical model of drug action presents a particular barrier to achieving these psychological effects and may even weaken them. The drug-centred model makes no claims that drugs are addressing a presumed underlying

biological problem, and therefore is theoretically more compatible with the development of the individual's own resources in a psychological approach. Coming to understand that depressive episodes, anxiety attacks, and psychotic episodes are usually meaningful reactions to abnormal or overwhelmingly stressful contexts, rather than being defects that just happen, may produce metalevel change and thus sustained recovery. Ideally, this becomes valuable knowledge about oneself on what to do less of and what to do more of, thus relating to one's emotions as the inner compass they fundamentally are in their primary form.

Thus, getting diagnosed and starting drug treatment may involve (or act as a stimulus to) a number of psychological and behavioural activities potentially relevant to improvement and recovery. These may be inherently related to the pill or 'the pill-intaking-behaviour' and the associated diagnostic rituals rather than the biological or psychoactive effects of the drugs, yet they are often attributed to the latter. Attributing improvement to these activities, rather than the effects of the substance, has the potential to facilitate an internal locus of control, to enhance metacognitive beliefs of controllability, emotional schemes of comprehensibility, sense of self-control, agency, and empowerment all of which can promote good mental health.

**Implications for coming off psychiatric drugs**

Acknowledging the drug-centred model has implications for psychiatric drug withdrawal. Removing an emotion regulation strategy, however maladaptive it may be, leaves the patient emotionally vulnerable and may force him/her back to the distressing state of experienced uncontrollability, incomprehensibility, excessive thoughts, and overwhelming emotions. As the psychoactive effects can only be expected to fade upon drug discontinuation, this transition from having one's mind slowed and emotions numbed to once again getting in touch with the normal, fluctuating, analysing, primarily negative, unmedicated human mind can be difficult. Such challenges of coming off psychiatric drugs are rarely discussed. These challenges are

compounded by the physiological withdrawal symptoms associated with withdrawal from many drugs,[162] and moreover withdrawal symptoms and underlying emotional fluctuations may be difficult to distinguish from each other. In our clinical experience and based on patients' experiences as expressed on online forums, an emotional 'rebound' may occur in which emotions become even more intense than they were in the first place. People withdrawing from SSRIs, for example, report how they become tearful and emotionally labile, and this may represent the body bouncing back from months or years of neurological effects that produce emotional suppression.[163]

Coming off psychiatric drugs may thus require the same transition from maladaptive to adaptive emotion regulation that constitutes recovery from psychopathology in general, including being able to accept, use, live with, and detach cognitively from strong emotions while withdrawal symptoms last. Psychotherapy may therefore be helpful for some patients when withdrawing from psychiatric drugs. It is also important to recognise that withdrawal symptoms may frequently be interpreted as signs of relapse, especially if people have accepted the medical model explanation that the drugs are reversing an underlying biological defect. In this situation, traditional cognitive reinterpretation techniques may be helpful.

## Implications for future research

Conceptual changes are needed in the way we understand psychiatric drugs. We urgently need to update the way drugs are named and classified and to abandon terms like 'antidepressant' and 'antipsychotics' that suggest drugs work through unproven targeted actions. Instead, we need to classify and name drugs according to the sort of psychoactive and physiological alterations they produce, including their effects on emotions. Qualitative research is needed to provide further information about the nature of these alterations, including more detail about the complex and sometimes subtle effects of different substances on our emotional responses. Research is also needed on how and why some patients experience these

psychoactive effects as helpful for addressing psychological symptoms. Furthermore, the impact of psychiatric drug treatment on metacognitive beliefs and emotional schemes should be investigated.

## Conclusion

Evidence does not support the medical, or disease-centred, model of psychiatric drug action, and the drug-centred model provides an alternative that is consistent with the recognised psychoactive effects of all psychiatric drugs. The drug-centred model suggests that the psychoactive effects are superimposed on psychopathological symptoms and thus act as a means of emotion regulation by replacing unwanted emotions and symptoms with a drug-induced state of emotional numbing, suppression, sedation, mental slowing, lethargy, etc. Psychiatric drugs should be prescribed and used with these mechanisms of action in mind, in appropriate – often shorter – duration, preferably in times of crisis, and with awareness of the potential negative long-term effects on the metacognitive beliefs and emotional schemes that appear to drive psychopathology. Given that many psychopathological states across diagnoses are characterised by uncontrollable, overwhelming, and incomprehensible emotions and excessive or intrusive thoughts (and the maladaptive emotion regulation strategies that follow), drug-induced states are often experienced as more emotionally appealing. However, that emotions and thoughts are uncontrollable, overwhelming, last indefinitely, escalate, and make no sense are beliefs that can be targeted and modified, and this introduces a potential conflict between the psychopharmacological and the psychological solutions to psychopathology. Continuous emotion regulation via an external substance - while treating symptoms and making patients feel better - risks confirming and reinforcing the problematic beliefs, thus violating the psychological principles and aims of lasting recovery.

This paradox delineates the different levels of the emotion regulation model of psychopathology, illustrating how interventions can target psychopathology in different ways. Furthermore, it highlights how the medical model and the drug-centred model may lead to contrasting

implications for the impact of drugs on emotion regulation strategies. The medical model obscures the way that psychiatric drugs impact on emotions both through their psychoactive effects and their symbolic, psychological, or placebo effects. This discourages both patients and prescribers from learning how to use drug-induced effects with caution and discrimination, and it obscures other factors contributing to improvement, including natural fluctuations, various psychological effects associated with the processes of diagnosis and prescription of medication, and active changes people make in their lives to address their underlying problem (whether the drug was involved in making them or not). Believing in the medical model of drug action may also introduce anxiety and catastrophizing of withdrawal symptoms when coming off drugs, potentially leading to a self-fulfilling pattern of relapse. The drug-centred model, by contrast, is transparent about the way psychiatric drugs act as emotion regulation strategies and highlights how psychiatric drug treatment needs to be informed also by emotion regulation research.

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**Table 1.** Outcomes of meta-analyses (including reanalyses) of RCTs comparing antidepressants with placebo

| Study | HAM-D | SMD |
|---|---|---|
| Kirsch 1998[39] | - | 0.39 |
| NICE 2004[66] | - | 0.34 |
| Moncrieff 2004[52] | - | 0.39 |
| Turner 2008[63] | - | 0.31 |
| Kirsch 2008[50] | 1.80 | 0.32 |
| Arroll 2009[65] | - | 0.32 |
| Fournier 2010[53] | 1.94 | 0.30 |
| Fountoulakis 2011[51] | 2.18 | 0.32 |
| Khin (FDA) 2011[54] | 2.50 | - |
| Gibbons 2012[55] | 2.56 | - |
| Jakobsen 2017[56] | 1.94 | 0.23 |
| Stone (FDA) 2018[62] | 1.80 | - |
| Furukawa 2018[164] | 1.62 | - |
| Cipriani 2018[57] | 2.50 | 0.30 |
| Munkholm 2019[60] | 1.97 | 0.29 |

**Table 1 legend:** SMD: Standardized mean difference; HAM-D: Hamilton Rating Scale for Depression.
Interpretation of SMD and HAM-D: The official cut-off to define clinical significance is three points on the HAM-D, however, no supporting evidence was cited when this value was chosen.[66] Studies comparing HAM-D with the Clinical Global Impression Scale (CGI) find that an improvement of three points on HAM-D (equivalent to an SMD of g=0.375) corresponds to 'no change' on the CGI, whereas an improvement of seven points (or SMD g=0.875) is required to be judged by an experienced clinician as having 'minimally improved' on the CGI. 'Much improved' on the CGI corresponds to 14 HAM-D points (or SMD g=1.75).[49,58] No meta-analysis has reached either cut-off for clinical significance defined in either way, thus leading to the conclusion that antidepressants do not outperform placebos, but that patients on placebo experience comparable improvement.

**Table 2.** The principal mental and physical alterations produced by psychiatric drugs

| Major drug class | Examples | Principal mental and physical alterations |
|---|---|---|
| Antipsychotics | Older antipsychotics (chlorpromazine, haloperidol, sulpiride), risperidone, amisulpiride | Sedation, emotional numbing, mental slowing and impairment, muscular rigidity (Parkinsonism), weight gain, akathisia |
| | Olanzapine, clozapine, meperone | Sedation, emotional numbing, mental slowing and impairment, increased appetite, substantial weight gain |
| | Quetiapine | Sedation, emotional numbing, mental slowing and impairment, modest weight gain |
| | Aripiprazole | Emotional numbing, lethargy, agitation at higher doses |
| Antidepressants | Tricyclic antidepressants | Sedation, impaired mental abilities, weight gain |
| | SSRIs | Lethargy, emotional numbing, occasional agitation especially in younger users |
| | SNRIs (Venlafaxine and duloxetine) | Lethargy, day-time drowsiness, emotional numbing |
| | Mirtazapine | Sedation, increased appetite, weight gain |
| Drugs used in manic depression/bipolar disorder | Lithium | Sedation, mental slowing and impairment, weight gain |
| | Sodium valproate, depakote | Sedation, mental slowing and impairment, weight gain |
| | Carbamazepine | Sedation, mental slowing and impairment, weight gain |
| | Lamotrigine | Sedation, mental slowing and impairment |
| Benzodiazepines and Z-drugs | Alprazolam, diazepam, oxazepam, chlordiazepoxide, clorazepate, zolpidem, Zopiclone | Sedation, mental and muscular relaxation, mental slowing and impairment |
| Stimulants | Amphetamine, methylphenidate/Ritalin | Increased alertness, heart rate and blood pressure, increased concentration and reduced activity at low doses, reduced exploratory behaviour, weight loss |

**Table 2 legend**: SSRI: Selective Serotonin Reuptake Inhibitor; SNRI: Serotonin-Norepinephrine Reuptake Inhibitor. This tables was reproduced from Moncrieff, J. (2020) A Straight Talking Introduction to Psychiatric Drugs, Second Edition, PCCS Books: Monmouth, UK (P 159-161).

**Box 1.** Examples of early descriptions of how psychiatric drugs were assumed to work

Winkelman on Chlorpromazine:
*'A pathological tranquillity of mind.'* (1957)[165]
*'… patients who had been severely agitated, anxious and belligerent became immobile, wax like, quiet, relaxed and emotionally indifferent.'* (1954)[166]

Scull on Chlorpromazine:
*'There is no thought that chlorpromazine is any cure for mental illness, but it can have great value if it relaxes patients and makes them accessible to treatment. The extremely agitated or anxious types often give up compulsive behavior, a surface symptom of their illness… It is as though the patients said, "I know there's something disturbing me, but I couldn't care less."'* (1954)[167]

Proceedings of the symposium held under the auspices of Smith, Kline & French laboratories:
*'The drugs could be used to attain a neuropharmacologic effect, not to cure a disease.'* (1955)[168]

Bradley on Benzedrine
*'… warned that the children's underlying physical and mental problems still needed careful psychosocial therapy from trained professionals.'* (1937)[169]

Delay & Deniker on Chlorpromazine:
*'The apparent indifference or the delay in response to external stimuli, the emotional and affective neutrality, the decrease in both initiative and preoccupation without alteration in conscious awareness or in intellectual faculties constitute the syndrome due to treatment.'* (1974)[170]

Lehmann on Chlorpromazine:
*'The aim is to produce a state of motor retardation, emotional indifference, and somnolence, and the dose must be increased accordingly as tolerance develops… The patients under treatment display a lack of spontaneous interest in their environment… they tend to remain silent and immobile when left alone and to reply to questions in a slow monotone… Some patients dislike their treatment and complain of their drowsiness and weakness. Some say they feel 'washed out,' as after an exhausting illness, a complaint which is indeed in keeping with their appearance.'* (1954)[171]

Elkes on Chlorpromazine:
*"It is important to stress that in no case was the content of the psychosis changed…The schizophrenic and paraphrenic patients continued to be subject to delusions and hallucinations though they appeared to be less disturbed by them."* (1954)[172]

Lehmann & Hanrahan on Chlorpromazine:
*"Many patients dislike the 'empty feeling' resulting from the reduction of drive and spontaneity which is apparently one of the most characteristic effects of this substance"* (1954)[171]

**Figure 1.** The causal relationship between beliefs, triggers, emotion regulation strategies, and psychopathology

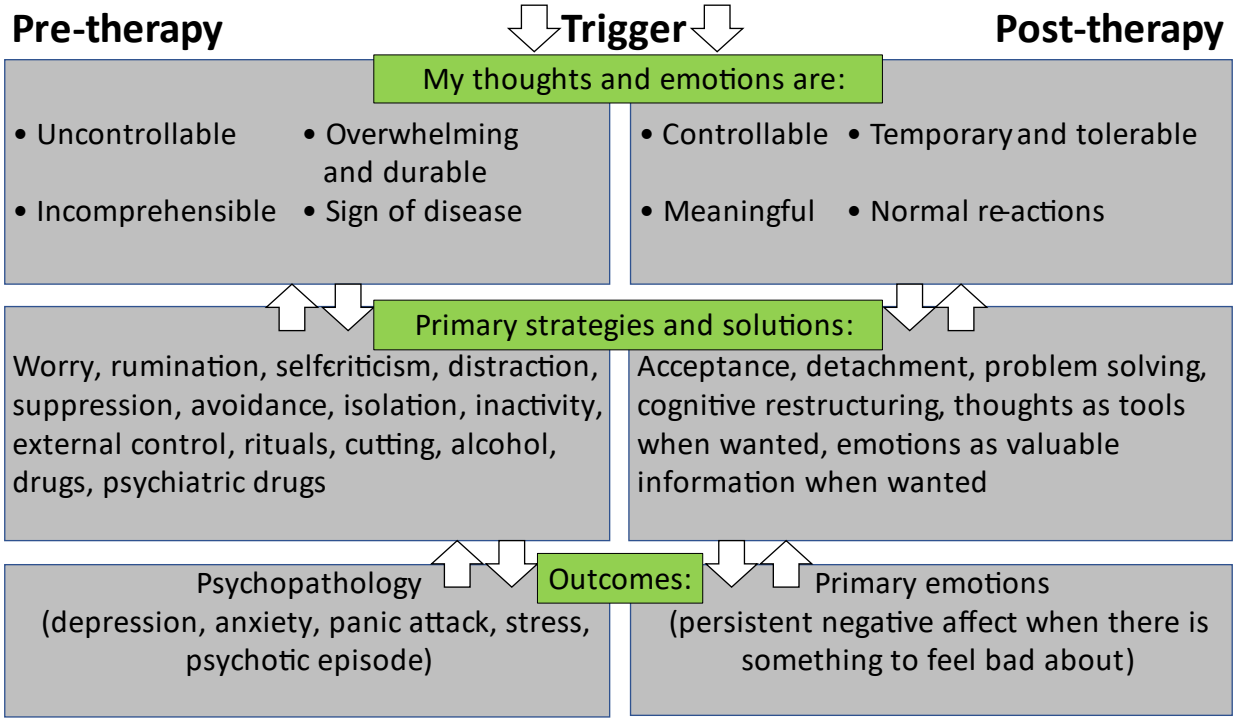


**Figure 1 legend:** The figure illustrates the causal and bidirectional relationships between metacognitive beliefs/emotional schemes, emotion regulation strategies, and psychopathology both before (left side) and after (right side) effective psychotherapy. Whether strong emotional states evolve into psychopathological states (e.g., a depressive episode, clinical anxiety, a panic attack, stress burnout, or a psychotic episode) depend on how they are regulated, and how they are regulated depends on what the individual thinks and believes about his/her thoughts and emotions. Primary use of maladaptive emotion regulation strategies (left side of the figure) backfires long-term, producing more negative affect while not effectively resolving the primary emotions. Primary use of adaptive emotion regulation strategies (right side of the figure) effectively resolves the primary emotions or at minimum does not result in additional negative affect and symptoms. However, the maladaptive emotion regulation strategies present, and are experienced as, solutions to the problems caused by holding problematic beliefs, e.g., of uncontrollability, durability, and incomprehensibility. The psychotherapeutic solution is to identify and modify these beliefs as a way of moving patients from a maladaptive to an adaptive emotion regulation style. The psychopharmacological solution – in a drug-centred model – is to add another emotion regulation strategy that operate within the set of problematic beliefs.