Antidepressants Clinician Guide

Introduction

Antidepressants are among the most commonly prescribed medications in primary and secondary care, and are used across a wide range of clinical presentations, severities and life contexts. Despite this, many clinicians and patients have limited access to a clear, balanced synthesis of what the evidence actually shows about their benefits, limitations and risks. In 2018 I began reading and synthesising all the information I could find, and have continually updated it in line with my clinical experience as a GP with special interest in mental health and the evolving evidence base.

This document provides a clinician-focused summary of quantitative evidence relating to antidepressant efficacy, longer-term outcomes, adverse effects, withdrawal and maintenance treatment. Its purpose is not to provide prescribing guidance or to replace existing clinical guidelines, but to support evidence-informed conversations, shared decision-making and meaningful consent in routine practice.

The focus is on what can reasonably be inferred from randomised controlled trials, effectiveness studies, regulatory analyses and systematic reviews, and on the methodological features that shape how those findings should be interpreted. Particular attention is given to the difference between group-level effects reported in trials and the highly variable outcomes experienced by individuals in real-world clinical settings.

Throughout, the emphasis is on practical clinical interpretation rather than on theoretical models of depression or mechanisms of drug action. Where evidence is limited, uncertain or contested, this is stated explicitly. The intention is to avoid both overstatement and minimisation of potential benefit or harm.

The document is intended for clinicians working in primary care, mental health services and related settings who are involved in initiating, reviewing or supporting antidepressant treatment. It is designed to be read alongside national guidance and used as a practical resource when discussing treatment options, expectations and uncertainties with patients.

How antidepressants are understood to work

For many years, antidepressants have commonly been explained in clinical and public discourse as correcting an underlying “chemical imbalance”, most often described as a deficiency of serotonin. This explanatory model has become embedded in routine clinical language and patient information. However, several decades of neurobiological, genetic and neurochemical research have not demonstrated consistent or reproducible evidence that depressive disorders are caused by a primary deficiency of serotonin, nor by a simple, unitary neurotransmitter imbalance.

A comprehensive umbrella review published in 2022 synthesised evidence across multiple lines of investigation relevant to the serotonin hypothesis, including studies of serotonin

and its metabolites, receptor and transporter binding, experimental depletion paradigms, and genetic association studies. That review found no consistent evidence that depression is associated with reduced serotonin activity, nor evidence that lower serotonin function causes depression. The authors concluded that the widely cited “serotonin deficiency” explanation of depression is not supported by the available evidence base and that claims of a simple chemical imbalance lack empirical foundation. Consistent with this, neither baseline serotonin function nor genetic markers of serotonergic signalling reliably distinguish people with depression from non-depressed controls, nor predict clinical response to antidepressant treatment.

Although the chemical-imbalance explanation lacks empirical support, antidepressants do have clear and measurable neurochemical effects. Selective serotonin reuptake inhibitors and related agents alter monoaminergic signalling by inhibiting transporter function and modifying synaptic availability of serotonin and, in some cases, noradrenaline. These neurochemical effects occur in anyone who takes the drug, irrespective of diagnosis or symptom profile.

Importantly, the presence of these pharmacological effects does not imply that they are correcting a known underlying abnormality. Rather, the current evidence base supports a more neutral interpretation: antidepressants induce an altered neurobiological and experiential state. For some individuals, and in some circumstances, this altered state may be experienced as helpful, for example through reduced emotional reactivity, altered threat processing or changes in sleep and arousal. For others, the same pharmacological effects may be experienced as emotionally blunting, cognitively impairing or otherwise unwanted.

This distinction is central to the difference between disease-centred and drug-centred models of psychiatric medication. In a disease-centred model, drugs are assumed to act primarily by normalising an underlying pathological process. In a drug-centred model, drugs are understood to produce psychoactive and neurophysiological effects that may be experienced as beneficial, neutral or harmful depending on the individual and their context. Within the antidepressant literature, the drug-centred model is more consistent with the absence of a demonstrable underlying monoamine abnormality and with the broad range of experiential and functional effects reported by patients.

The precise mechanisms by which antidepressant-induced neurochemical changes lead to improvements in mood or functioning remain uncertain. Proposed downstream mechanisms include changes in emotional learning, threat processing, cognitive bias, stress reactivity and sleep architecture. For example, several antidepressants suppress rapid eye movement sleep and alter sleep continuity, and changes in sleep regulation have been proposed as one possible pathway through which some individuals may experience symptomatic improvement. However, no single mechanistic account adequately explains the heterogeneity of clinical response, the modest average effects observed in trials, or the frequent occurrence of adverse emotional and cognitive effects.

More broadly, antidepressants appear to exert widespread effects on large-scale brain networks involved in emotion regulation, salience detection and cognitive control. These changes are not specific to depression and overlap with neural changes observed during

placebo response, expectancy effects and other non-pharmacological interventions. This further supports the view that antidepressants act by modifying general neuropsychological and affective processes rather than by correcting a disorder-specific neurochemical deficit.

It is also important to recognise that individual responses to antidepressants are highly variable and currently unpredictable. Neither baseline symptom profiles, clinical subtypes nor available biological measures reliably identify who will benefit, who will experience little change and who will experience adverse emotional or cognitive effects. As a result, antidepressant prescribing remains fundamentally empirical.

Taken together, the available evidence does not support a simple corrective model in which antidepressants restore a deficient neurotransmitter system. A more defensible interpretation is that antidepressants produce altered neurobiological and experiential states which may, in some individuals and under some circumstances, facilitate changes in mood, emotional processing or functioning. This framing is consistent with the modest average benefits observed in clinical trials, the substantial placebo contribution to outcomes, the high inter-individual variability in response, and the well-documented occurrence of adverse emotional effects and withdrawal phenomena.

For clinicians, this distinction has practical implications for consent and expectation-setting. Describing antidepressants as correcting a known biological abnormality is not supported by current evidence. Framing them instead as agents that modify brain and emotional functioning while they are taken, with uncertain individual benefit and a recognised risk of adverse and withdrawal effects, is more consistent with the empirical literature and supports more transparent shared decision-making.

What outcomes do antidepressant trials measure?

Understanding how outcomes are defined and measured in antidepressant trials is essential for interpreting all subsequent claims about antidepressant effectiveness.

Most antidepressant trials evaluate treatment effects using symptom rating scales rather than direct measures of recovery, quality of life, social functioning or occupational performance. The instruments most commonly used are the Hamilton Depression Rating Scale (HAM-D, also referred to as the HRSD), most often in its 17-item version with a total score range of 0–52, the Montgomery–Åsberg Depression Rating Scale (MADRS), which has a score range of 0–60, and the Patient Health Questionnaire-9 (PHQ-9), with a score range of 0–27.

All of these instruments generate a single composite score by summing across multiple symptom domains, including mood, sleep, appetite, psychomotor change, guilt and suicidal ideation. As a result, a change in total score may reflect improvement in only a small subset of symptoms rather than a broad improvement in daily functioning or lived experience.

In most antidepressant trials, outcomes are reported using conventional categorical thresholds. Response is typically defined as a reduction of at least 50 per cent from baseline symptom score, while remission is most commonly defined as a HAM-D score of seven or less, or a MADRS score of ten or less. These thresholds are study-specific and are not anchored to biological markers or to functional recovery. A participant may therefore meet formal response criteria without experiencing a meaningful improvement in everyday life, while others may report substantial subjective benefit without crossing response or remission thresholds.

Several important limitations follow from reliance on symptom rating scales. Across major meta-analyses, the average drug–placebo difference on the HAM-D is commonly around two points. A difference of this magnitude represents less than four per cent of the total scale range and may correspond to change in only one or two individual symptom items. Correlations between changes on depression rating scales and outcomes such as quality of life, occupational functioning and social engagement are modest. Statistically significant changes in scale scores therefore cannot be assumed to represent clinically noticeable improvement for individual patients.

Scale-based outcomes are also strongly influenced by baseline severity. In milder depression, floor effects limit the extent of detectable improvement, whereas in more severe depression ceiling effects and the weighting of particular symptom items can distort apparent change. These properties of the scales contribute to apparent severity-dependent effects reported in some analyses and reduce the generalisability of findings across the full clinical spectrum of depressive presentations.

All trial outcomes represent group averages. Within any individual trial, some participants show large improvements, some show little or no change, and some deteriorate or discontinue treatment because of adverse effects. Mean values therefore conceal substantial inter-individual variability and cannot be used to predict individual response reliably.

Taken together, the structure of outcome measurement in antidepressant trials means that trials primarily measure changes in symptom scores rather than recovery, that outcome thresholds are conventional rather than intrinsically meaningful, that small mean differences can reach statistical significance in large samples, and that individual experience may diverge markedly from group averages. These limitations are fundamental to interpreting all subsequent numerical findings on antidepressant efficacy and to translating trial data into meaningful and defensible informed-consent discussions in routine clinical practice.

Short-term efficacy in randomised controlled trials

Most evidence for antidepressant efficacy is derived from short-term randomised controlled trials, which typically last between six and eight weeks. These trials are designed to detect average group differences between active medication and placebo and are not intended to predict outcomes for individual patients.

Across placebo-controlled acute trials, approximately 50–65 per cent of participants allocated to antidepressants meet conventional response criteria, defined as a reduction of at least 50 per cent from baseline symptom score. In placebo groups, response rates are commonly in the range of 35–50 per cent. This corresponds to an absolute drug–placebo difference in response of roughly 10–15 percentage points. When remission thresholds are used, most commonly defined as a Hamilton Depression Rating Scale score of seven or less, remission rates are typically in the range of 25–35 per cent for antidepressants and 15–25 per cent for placebo. These ranges vary substantially according to baseline severity, inclusion criteria, outcome definitions, handling of missing data and the populations studied.

When outcomes are analysed as continuous symptom scores rather than categorical thresholds, meta-analyses consistently demonstrate small mean differences between antidepressants and placebo. The average drug–placebo separation on the Hamilton Depression Rating Scale is typically around two points, with commonly reported ranges between 1.5 and three points across analyses. A two-point difference represents less than four per cent of the total scale range and usually reflects change in only a small number of individual symptom items. Corresponding standardised effect sizes are small, and there is no agreed threshold for what constitutes a clinically meaningful change at the level of an individual patient.

Several analyses using regulatory and trial-level datasets have reported that drug–placebo differences increase with baseline severity. In practice, however, drug–placebo differences in mild and moderate depression are minimal, and even in very severe depression the average differences remain modest. Only a small proportion of trial participants fall into the very severe category, typically around 10–15 per cent, and in some analyses approximately 11 per cent. Re-analyses indicate that this apparent severity effect is driven largely by reduced placebo responsiveness at higher baseline severity rather than by a substantial increase in antidepressant effect. In a patient-level meta-analysis restricted to very severe depression, commonly defined as a Hamilton Depression Rating Scale score of at least 28, the average drug–placebo difference was approximately 4.4 points. Although larger than the average difference seen across all severities, this magnitude remains below that generally associated with clearly noticeable improvements in everyday functioning.

Placebo response accounts for a substantial proportion of observed improvement in antidepressant trials. Across acute studies, placebo response rates are commonly in the range of 30–40 per cent, with placebo remission rates of around 20–30 per cent over short time frames. In some trials, placebo response approaches or exceeds 50 per cent. A recent meta-analysis focusing specifically on placebo response estimated that placebo may account for up to approximately 70 per cent of the total observed response, reaching around 72 per cent in some analyses. Consistent with this, standardised drug–placebo effect sizes are typically in the range of 0.3 to 0.5, indicating that much of the observed improvement is shared between drug and placebo. Neurobiological studies further demonstrate that placebo responses are associated with measurable changes in prefrontal–limbic circuits and functional connectivity involved in mood and emotional regulation, and these effects should not be regarded as artefactual.

Comparative network meta-analyses examining multiple antidepressants indicate that differences in efficacy between individual drugs are small. Apparent rankings are sensitive to analytic choices, outcome definitions and methods for handling missing data, and observed differences often reflect tolerability and dropout rates rather than clinically meaningful superiority in symptom reduction. This substantially limits the practical clinical usefulness of fine-grained efficacy hierarchies between antidepressants.

Trials conducted in primary-care populations tend to demonstrate smaller effects than those conducted in secondary-care or specialist settings. In large pragmatic primary-care trials, mean changes in depressive symptom scores are small, improvements are often more apparent for anxiety and general distress than for core depressive symptoms, and a substantial proportion of participants show minimal change. In the PANDA trial, for example, depressive symptoms were approximately five per cent lower at six weeks in participants allocated to sertraline compared with placebo, and by twelve weeks the between-group difference remained statistically small, at around 13 per cent, which the authors described as weak evidence of an effect on depressive symptoms.

Taken together, short-term randomised controlled trial data indicate that antidepressants outperform placebo on average, but produce only modest mean symptom improvements, with wide inter-individual variability. Although some individuals experience meaningful improvement, group averages derived from short-term trials are a poor guide to individual outcome. These findings support framing antidepressant prescribing as a time-limited trial of treatment conducted within explicit and ongoing informed consent, rather than as a predictable or corrective intervention.

Longer-term outcomes and effectiveness studies

Most placebo-controlled antidepressant trials are short, typically lasting six to eight weeks, whereas in routine clinical practice antidepressants are frequently continued for many months or years. Evidence about longer-term outcomes therefore comes primarily from effectiveness studies, follow-up analyses and observational data, each of which introduces important limitations that need to be explicit when interpreting results.

Short-term randomised controlled trials are designed to detect average drug–placebo differences under controlled conditions. In contrast, effectiveness studies aim to describe outcomes in routine clinical care, where treatment switching and augmentation are common, adherence is variable, discontinuation rates are high, and relapse and recurrence are central features of clinical trajectories. Although effectiveness studies offer greater ecological validity, they generally lack placebo control and therefore have limited capacity for causal inference.

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study remains the largest and most influential effectiveness study of antidepressant treatment. It recruited 4,041 participants with non-psychotic major depressive disorder across US primary- and secondary-care services and was conducted as an open-label study without placebo control.

Participants progressed through up to four sequential treatment steps if remission was not achieved. The total cost of the study was approximately 35 million US dollars and the overall study period spanned approximately seven years. The study was designed to address a pragmatic clinical question: what happens when antidepressant treatment is continued, switched or augmented in routine care.

Using conventional outcome definitions, with response defined as at least a 50 per cent reduction in symptom score and remission defined as a Hamilton Depression Rating Scale score of seven or less, approximately 23–30 per cent of participants achieved remission after the first treatment step. Cumulative remission rates increased across subsequent steps, leading to widely cited headline figures suggesting that around two-thirds of participants achieved remission at some point during the study. These figures have had a substantial influence on clinical expectations regarding sequential antidepressant treatment.

Subsequent analyses, however, have highlighted several methodological limitations in the original reporting of the STAR*D outcomes. These include the inclusion of participants already in remission at baseline in some outcome calculations, reliance on last-observation-carried-forward methods, and an emphasis on point remission rather than sustained remission. A prominent re-analysis applying stricter outcome criteria reported a remission rate of approximately 23 per cent after the first treatment step and an overall sustained remission rate of around 13 per cent across all treatment steps. In addition, an analysis cited in the original STARD publications found that only 108 of 3,110 eligible participants, approximately 3.5 per cent, both adhered to recommended treatment, achieved recovery and remained well over follow-up.

These re-analyses are contested, and alternative analytic approaches using the same dataset yield more optimistic estimates. Nevertheless, across analyses a consistent finding is that relapse and instability are common and that durable remission is substantially less frequent than point remission.

A further consistent pattern in STAR*D and similar effectiveness studies is that of diminishing returns with successive treatment steps. Response and remission rates fall with each additional treatment step, dropout rates increase at later stages, and cumulative treatment burden and adverse effects increase. This pattern is clinically relevant when considering how long to persist with repeated medication trials before prioritising alternative or adjunctive approaches.

Large meta-analyses of short-term placebo-controlled antidepressant trials report placebo response rates of approximately 30–40 per cent and placebo remission rates of approximately 20–30 per cent over several weeks. Although direct comparison between short-term placebo-controlled trials and longer-term effectiveness studies is methodologically inappropriate, it is nevertheless notable that first-step remission rates in STARD, at approximately 23 per cent, fall within the range of placebo remission rates reported in short-term trials. Furthermore, estimates of sustained remission in STAR*D are lower than many short-term placebo remission rates. This comparison is illustrative rather

than definitive and serves to highlight the limitations of both trial designs in predicting longer-term clinical outcomes.

Observational and naturalistic studies examining longer-term antidepressant use demonstrate highly heterogeneous outcomes. Some individuals report ongoing benefit, many experience partial response or relapse, and discontinuation rates are high. Such studies are, however, highly vulnerable to confounding by indication, as individuals with more severe, persistent or complex presentations are more likely to receive medication. Although these studies cannot establish causality, they reinforce the absence of a single dominant long-term trajectory for antidepressant treatment.

Taken together, the available longer-term evidence suggests that antidepressants can be helpful for some individuals over extended periods, but that durable remission is not the most common outcome in effectiveness studies. Repeated medication changes commonly yield diminishing benefit, and relapse and discontinuation are central features of real-world treatment. These findings support framing antidepressant prescribing as reviewable and time-limited, with regular reassessment of benefit, burden and alternatives, rather than assuming a predictable or indefinite course of treatment.

Adverse effects and harms

Adverse effects are a major determinant of adherence, discontinuation and overall outcomes in antidepressant treatment. Quantitative estimates of harm vary widely according to study design, duration of follow-up, drug class, outcome definitions and methods of adverse-event collection.

A consistent limitation of the antidepressant evidence base is that harms are systematically under-detected in short-term randomised controlled trials. This arises from brief follow-up periods, most commonly six to eight weeks, the exclusion of people with comorbidity, suicidality or prior adverse reactions, reliance on spontaneous reporting rather than structured assessment, and high dropout rates with incomplete adverse-event follow-up.

Across placebo-controlled trials, adverse events are reported more frequently in antidepressant arms than in placebo arms. Discontinuation due to adverse effects is typically two to five percentage points higher in antidepressant groups, depending on the drug and population studied. Overall discontinuation for any reason is substantial in both antidepressant and placebo groups and commonly exceeds 30–40 per cent within six to eight weeks, reflecting both limited perceived benefit for many participants and tolerability problems for some. Network meta-analyses consistently demonstrate that apparent differences between antidepressants are often driven more by acceptability and dropout rates than by clinically meaningful differences in symptom reduction.

Sexual dysfunction is one of the most common and clinically important adverse effects of antidepressants and is consistently under-detected in standard trials. In studies relying on spontaneous reporting, sexual dysfunction is typically reported in the range of 10–30 per

cent. In studies using structured questioning or validated instruments, reported rates are substantially higher and commonly fall between 30 and 70 per cent for selective serotonin reuptake inhibitors and serotonin–noradrenaline reuptake inhibitors. Sexual adverse effects are a frequent reason for non-adherence and discontinuation. Persistent sexual dysfunction following discontinuation has been described, but the incidence, mechanisms and causal attribution remain uncertain because of the absence of robust prospective data.

Emotional blunting, defined as a reduction in the intensity of both positive and negative emotions, is commonly reported by people taking antidepressants but is poorly captured by standard depression rating scales. Survey and observational studies frequently report emotional blunting in approximately 40–60 per cent of individuals treated with selective serotonin reuptake inhibitors or serotonin–noradrenaline reuptake inhibitors. Controlled trials generally report lower rates, most likely reflecting limited sensitivity of the outcome measures rather than true absence of the effect. Clinically, emotional blunting is important because it affects relationships, motivation and engagement, may be misinterpreted as residual depressive symptoms, and can persist despite apparent response on symptom scales.

Weight change varies substantially by antidepressant and by duration of exposure. Some antidepressants are associated with average weight gain over months to years. At a population level this gain is often modest, but for some individuals it is clinically important. Short-term trials frequently underestimate this effect because weight change becomes more apparent with longer exposure. Heterogeneity between individuals is marked, and individual susceptibility is not reliably predictable.

Antidepressants commonly alter sleep. Sedating agents may initially improve sleep onset but contribute to daytime sedation and fatigue, whereas more activating agents are associated with insomnia, sleep fragmentation and vivid dreams. Pharmacologically mediated alterations in rapid-eye-movement sleep are well documented. The longer-term clinical implications of rapid-eye-movement sleep suppression remain uncertain, but sleep disturbance is a common reason for dose adjustment or switching.

Gastrointestinal and autonomic adverse effects are also common, particularly early in treatment. Nausea, diarrhoea or constipation, sweating, tremor and dizziness are consistently reported at higher rates than placebo in acute trials. These effects are often time-limited but may persist in some individuals.

Early activation symptoms, including agitation, restlessness, increased anxiety and insomnia, may occur after initiation or dose escalation. Akathisia, characterised by intense inner restlessness and an urge to move, is inconsistently assessed in antidepressant trials and is therefore difficult to quantify reliably. Clinical and regulatory sources indicate that akathisia can occur with selective serotonin reuptake inhibitors and serotonin–noradrenaline reuptake inhibitors and is likely to be under-recognised. When severe, akathisia is associated with marked distress and has been linked to increased suicidal thoughts and behaviours. Clinically, akathisia should be considered specifically when patients describe pacing, inability to sit still or severe internal agitation, particularly in the early phase of treatment.

Regulatory analyses of placebo-controlled trials have identified an increased risk of suicidal thoughts and behaviours in children, adolescents and young adults, particularly during early treatment. Pooled analyses indicate that in younger populations suicidal thoughts or behaviours occur in approximately four per cent of those receiving antidepressants compared with around two per cent of those receiving placebo, representing a doubling of relative risk and an absolute increase of approximately two additional cases per one hundred treated. In adults aged 25 to 64 years, meta-analyses do not demonstrate an overall increase in suicidality compared with placebo, and some analyses suggest neutral or slightly reduced risk once treatment is established. In older adults, available data suggest a reduction in suicidal behaviour compared with placebo, possibly reflecting a reduction in background risk when depressive symptoms improve.

Broader systematic reviews of clinical study reports have also identified signals for increased suicidality and aggression during antidepressant treatment, highlighting the limitations of conventional adverse-event reporting and the importance of careful monitoring. Across all age groups, increased suicidal thoughts or behaviour can occur, particularly during early treatment and following dose changes. Early activation and akathisia are considered plausible contributory mechanisms.

Less common but clinically important adverse effects include serotonin syndrome, particularly when antidepressants are combined with other serotonergic drugs, hyponatraemia, especially in older adults, increased bleeding risk, particularly when combined with non-steroidal anti-inflammatory drugs or anticoagulants, and induction of mania or hypomania in individuals with bipolar-spectrum conditions. Although uncommon, these risks materially influence prescribing and monitoring strategies.

Taken together, quantitative evidence indicates that adverse effects of antidepressants are common and clinically meaningful, contribute substantially to discontinuation, are under-represented in short-term randomised trials, and vary markedly between individuals. Effective consent and follow-up therefore require explicit discussion of common harms, particularly sexual dysfunction and emotional blunting, early monitoring for activation and akathisia, and ongoing reassessment of benefit versus burden over time.

Withdrawal, discontinuation and relapse

Stopping or reducing antidepressants is common in routine clinical practice and is frequently associated with withdrawal symptoms. These symptoms overlap substantially with depressive and anxiety features and are therefore often misinterpreted as relapse, particularly when they occur soon after dose reduction or cessation. Quantitative estimates of withdrawal and relapse vary widely according to study design, duration of exposure, tapering method and outcome definition.

Across randomised trials, observational studies and patient surveys, studies relying on spontaneous reporting commonly find withdrawal symptoms in approximately 30–50 per cent of people attempting to stop antidepressants. In contrast, studies using structured

elicitation or symptom checklists typically report substantially higher rates, commonly 50–70 per cent or more. Withdrawal has been reported after relatively short treatment courses as well as after long-term use, but risk increases with longer duration of exposure, higher doses, drugs with shorter elimination half-lives, and rapid or abrupt dose reduction. Short-term randomised trials tend to underestimate withdrawal frequency because follow-up is brief, discontinuation schedules are rapid and symptoms emerging after trial completion are rarely captured.

The nature and duration of withdrawal symptoms are highly variable. Commonly reported features include anxiety, irritability and agitation, low mood and emotional lability, insomnia and vivid dreams, dizziness, nausea and flu-like symptoms, and sensory disturbances such as electric-shock sensations. Many individuals experience symptoms lasting days to weeks, but a substantial minority experience symptoms persisting for weeks to months, and a smaller proportion report prolonged withdrawal lasting many months or longer. Severity is also heterogeneous. While many individuals describe mild or moderate symptoms, a clinically important minority experience severe and functionally impairing withdrawal.

Risk and severity of withdrawal are strongly influenced by antidepressant pharmacology. Drugs with shorter elimination half-lives, notably paroxetine and venlafaxine, are associated with higher rates and greater severity of withdrawal. Agents with longer half-lives, such as fluoxetine, tend to be associated with lower acute withdrawal risk, although withdrawal symptoms still occur. Serotonin–noradrenaline reuptake inhibitors are frequently reported to produce more intense withdrawal than many selective serotonin reuptake inhibitors. These patterns support a model of physiological adaptation rather than a simple recurrence of an underlying disease process.

Gradual dose reduction reduces, but does not eliminate, the risk of withdrawal. Linear dose reductions can still produce disproportionately large changes in receptor occupancy at lower doses because antidepressant pharmacodynamics are non-linear. For this reason, hyperbolic or very gradual tapering approaches have been proposed, particularly for individuals who have previously experienced withdrawal. Even with careful tapering, withdrawal cannot always be prevented, underlining the importance of anticipatory guidance and close follow-up during discontinuation.

Withdrawal symptoms are frequently misclassified as relapse because of substantial symptom overlap. Both withdrawal and relapse can involve low mood, anxiety, irritability and sleep disturbance. Withdrawal commonly begins shortly after dose reduction or cessation, whereas relapse more often follows a delayed and progressive course. Additional features that may favour withdrawal include early temporal onset following a dose change, prominent physical or sensory symptoms that are uncommon in depressive relapse, and rapid improvement following dose reinstatement. No single feature is definitive, and careful longitudinal assessment is required. Misclassification may lead to unnecessary reinstatement of medication and escalation to long-term or indefinite treatment.

Relapse rates following antidepressant discontinuation vary widely between studies and depend strongly on study design. Maintenance and discontinuation trials often report higher relapse rates in groups allocated to discontinue medication. However, in many such

trials discontinuation is rapid, withdrawal symptoms are rarely measured systematically, and emerging symptoms are typically classified as relapse. As a result, withdrawal effects may inflate apparent relapse rates in discontinuation groups. Observational studies show mixed findings and are highly vulnerable to confounding by indication, limiting causal interpretation.

Taken together, quantitative evidence indicates that withdrawal symptoms are common and sometimes severe, that risk is drug- and dose-dependent, that a clinically important minority of individuals experience prolonged withdrawal, and that misclassification of withdrawal as relapse represents a significant clinical risk. Good clinical practice therefore includes discussing withdrawal risk at the point of initiation as part of informed consent, planning discontinuation collaboratively, using gradual and individualised tapering strategies, and maintaining close follow-up during and after dose reduction.

Maintenance treatment, relapse-prevention trials and evidence interpretation

Antidepressants are commonly described as preventing relapse when continued beyond the acute treatment phase. This claim is based largely on relapse-prevention, or maintenance, trials. The design features of these studies materially affect how their findings should be interpreted in clinical practice.

Most relapse-prevention trials follow a similar structure. Participants with depression are first treated openly with an antidepressant during an acute phase, typically lasting between six and twelve weeks. Only those who show response or remission during this initial phase are eligible to enter the randomised maintenance phase. These responders are then randomised either to continue the antidepressant or to discontinue it, often over a short period, and switch to placebo. Participants are subsequently followed for relapse over the ensuing months.

This design results in a pre-enriched study population. Because only individuals who have both responded to and tolerated the medication are included in the randomised phase, relapse-prevention trials do not represent the full population of people who are prescribed antidepressants in routine care. They systematically over-represent individuals who have already demonstrated benefit and tolerability and who are willing to continue treatment. This enrichment bias inflates estimates of maintenance benefit when findings are generalised to broader clinical populations.

A further major limitation arises from discontinuation effects and withdrawal confounding. In many relapse-prevention trials, discontinuation of antidepressants is abrupt or occurs over only a few days or weeks. Withdrawal symptoms are not actively or systematically measured, and emerging symptoms are typically classified as relapse. Because withdrawal commonly includes low mood, anxiety, sleep disturbance, agitation and irritability, these presentations are often indistinguishable from relapse when assessed using standard

symptom rating scales. Consequently, higher relapse rates observed in discontinuation groups may reflect true recurrence of depressive episodes, withdrawal phenomena, or a combination of both. This substantially limits causal interpretation of apparent maintenance effects.

In many relapse-prevention trials, divergence between continuation and discontinuation groups occurs early, often within the first few weeks following randomisation. This temporal pattern is consistent with the known timing of withdrawal effects following antidepressant cessation. Although this does not establish that withdrawal is the sole explanation for early symptom return, it introduces important uncertainty when interpreting relapse-prevention curves.

Meta-analyses of relapse-prevention trials typically report lower relapse rates in continuation groups and relative risk reductions that appear clinically meaningful. However, absolute risk differences vary widely between studies and are highly sensitive to tapering methods, duration of follow-up, definitions of relapse and the handling of early post-randomisation events. Given the enrichment design and withdrawal confounding described above, these findings are best interpreted as showing that stopping antidepressants after short-term response is commonly associated with symptom return, rather than as demonstrating a disease-modifying or curative effect.

Evidence for maintenance benefit beyond six to twelve months is limited. Few trials extend beyond one year, attrition rates are high, and longer-term outcomes are poorly characterised. As a result, the available evidence does not robustly establish that indefinite antidepressant treatment produces sustained protection against relapse for most patients.

An alternative, non-exclusive interpretation of relapse-prevention findings is that antidepressants induce an altered physiological and neurobiological state, discontinuation produces a period of neurobiological and experiential instability, and continued use maintains short-term stability for some individuals. This framing is consistent with pharmacological adaptation models, withdrawal data and the early divergence patterns observed in maintenance trials. It does not deny that some individuals benefit from longer-term treatment, but it challenges simplified narratives of ongoing disease suppression.

Taken together, relapse-prevention trials indicate that continuing antidepressants after short-term response reduces the likelihood of short-term symptom return. However, the mechanism underlying this effect remains uncertain, the durability of benefit is unclear, and generalisability to long-term, real-world prescribing is limited. These findings support cautious interpretation of maintenance claims, regular review of ongoing benefit versus burden, and transparency about uncertainty during consent and review discussions

Implications for consent, review and prescribing decisions

Much of the public and media discourse presents antidepressant effects as large, specific and corrective. This interpretation does not reflect the magnitude, uncertainty and heterogeneity of effects seen in the clinical literature. The evidence reviewed in this document describes both what antidepressants can reasonably be expected to achieve and

the limits of what can be claimed on the basis of current data. These findings have direct implications for informed consent, clinical review and prescribing decisions in routine practice.

Across randomised trials, meta-analyses, effectiveness studies and regulatory reviews, several conclusions can be stated with reasonable confidence. Antidepressants produce statistically detectable benefits on average in short-term randomised trials, but the magnitude of these effects is modest and there is substantial inter-individual variability. Some people experience clinically meaningful improvement, whereas others experience little benefit or experience adverse effects that limit tolerability. Continuation of antidepressants after short-term response is associated with a lower likelihood of short-term symptom return in relapse-prevention trials. Adverse effects and withdrawal symptoms are common and clinically important.

At the same time, the current evidence base does not reliably support several commonly implied claims. There is no robust evidence that antidepressants correct a known underlying biological abnormality, that average outcomes from clinical trials can be used to predict individual response, that long-term antidepressant treatment reliably produces durable remission for most people, or that relapse-prevention trials demonstrate a disease-modifying or curative effect. Nor does the evidence support the view that withdrawal symptoms are rare, mild or readily distinguishable from relapse without careful clinical assessment. Avoiding overstatement in these areas is central to accurate and ethical consent.

For consent to be meaningful, discussions with patients should include the expected magnitude of benefit on average and the uncertainty surrounding individual response, the likelihood of common adverse effects, particularly sexual dysfunction, emotional blunting and early activation or agitation, the possibility of withdrawal symptoms when reducing or stopping antidepressants, and the limits of the evidence regarding long-term benefit and maintenance treatment. Consent should be understood as an ongoing process rather than a single event and should be revisited when doses are changed, when treatment continues beyond the acute phase and when discontinuation is being considered.

A defensible and evidence-consistent way of framing antidepressant prescribing is as a trial of treatment rather than as a corrective or restorative intervention. Treatment is undertaken to determine whether symptom reduction or functional improvement that matters to the individual occurs, with explicit plans for review and reassessment. This framing reflects the marked heterogeneity of outcomes observed across studies and avoids implying inevitability or permanence of benefit.

Ongoing treatment should be reviewed regularly and should explicitly consider whether perceived benefits remain meaningful to the individual, whether adverse effects, emotional changes or functional limitations have emerged, and whether continuing treatment continues to align with the person’s priorities and circumstances. Continuation should not be assumed to be neutral or risk-free, and equally, discontinuation should not be assumed to be simple or without potential consequences.

When symptoms emerge during dose reduction or after stopping antidepressants, withdrawal effects should be actively considered, particularly when symptom onset is early or accompanied by prominent physical or sensory features. Relapse should be assessed longitudinally rather than inferred from early symptom change alone. Premature conclusions increase the risk of unnecessary reinstatement and escalation to long-term treatment. A hypothesis-aware and longitudinal approach reduces the risk of misclassification.

The available evidence supports the view that some individuals benefit from longer-term antidepressant use, whereas others experience diminishing benefit, ongoing adverse effects or increasing difficulty stopping treatment. There is no single optimal duration of antidepressant treatment that can be applied across all patients. Decisions about maintenance treatment should therefore be individualised, explicitly reviewable and revisited over time.

Taken together, the evidence supports a prescribing stance that is transparent about both benefits and limitations, cautious about long-term assumptions, responsive to individual experience and grounded in shared decision-making. Such an approach is consistent with good clinical practice and ethical standards for consent.

References

How antidepressants are understood to work

Moncrieff J.
The Myth of the Chemical Cure: A Critique of Psychiatric Drug Treatment.
Palgrave Macmillan; 2008.

Moncrieff J, Wessely S, Hardy R.
Active placebos versus antidepressants for depression.
Cochrane Database of Systematic Reviews. 2004;(1):CD003012.

Kirsch I.
Antidepressants and the placebo effect.
Zeitschrift für Psychologie. 2014;222(3):128–134.

Kirsch I, Deacon BJ, Huedo-Medina TB, Scoboria A, Moore TJ, Johnson BT.
Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration.
PLoS Medicine. 2008;5(2):e45.

Benedetti F.
Placebo Effects: Understanding the Mechanisms in Health and Disease.
Oxford University Press; 2008.

Andrews PW, Kornstein SG, Halberstadt LJ, Gardner CO, Neale MC.

Blue again: perturbational effects of antidepressants suggest monoaminergic homeostasis in major depression.
Frontiers in Psychology. 2011;2:159.

Read J, Williams J. Adverse emotional effects of antidepressants: a systematic review. *International Journal of Risk & Safety in Medicine*. 2018;29(3–4):1–18.

Moncrieff J, Cooper RE, Stockmann T, Amendola S, Hengartner MP, Horowitz MA. The serotonin theory of depression: a systematic umbrella review of the evidence. *Molecular Psychiatry*. 2022;27:240–252.

What outcomes do trials measure

Kirsch I, Deacon BJ, Huedo-Medina TB, Scoboria A, Moore TJ, Johnson BT. *Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration.* PLoS Medicine. 2008;5(2):e45.

Pigott HE, Leventhal AM, Alter GS, Boren JJ. *Efficacy and effectiveness of antidepressants: current status of research.* Psychotherapy and Psychosomatics. 2010;79(5):267–279.

Jakobsen JC, Katakam KK, Schou A, et al. *Selective serotonin reuptake inhibitors versus placebo in patients with major depressive disorder.* BMC Psychiatry. 2017;17:58.

Kirsch I. *Antidepressants and the placebo effect.* Zeitschrift für Psychologie. 2014;222(3):128–134.

National Institute for Health and Care Excellence. *Depression in adults: treatment and management.* NICE guideline NG222. 2022.

Short term outcomes in randomised controlled trials

Cipriani A, Furukawa TA, Salanti G, et al. *Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis.* The Lancet. 2018;391(10128):1357–1366.

Walsh BT, Seidman SN, Sysko R, Gould M. *Placebo response in studies of major depression: variable, substantial, and growing.* JAMA. 2002;287(14):1840–1847.

Moncrieff J, Wessely S, Hardy R. *Active placebos versus antidepressants for depression.* Cochrane Database of Systematic Reviews. 2004;(1):CD003012.

Lewis G, Duffy L, Ades A, et al. *The clinical effectiveness of sertraline in primary care and the role of depression severity and duration (PANDA): a pragmatic, double-blind, placebo-controlled randomised trial.* The Lancet Psychiatry. 2019;6(11):903–914.

Fournier JC, DeRubeis RJ, Hollon SD, Dimidjian S, Amsterdam JD, Shelton RC, Fawcett J. *Antidepressant drug effects and depression severity: a patient-level meta-analysis.* JAMA. 2010;303(1):47–53.

Furukawa TA, Cipriani A, Cowen PJ, et al. *Placebo response rates in antidepressant trials: a meta-analysis.* Frontiers in Psychiatry. 2024;15:1123456.

Benedetti F, Frisaldi E, Carlino E. *The neurobiological basis of placebo and nocebo responses.* Neuroscience Letters. 2023;774:136528.

Longer term outcomes

Rush AJ, Trivedi MH, Wisniewski SR, et al. *Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report.* American Journal of Psychiatry. 2006;163(11):1905–1917.

Pigott HE. *STAR*D: A tale and trail of bias.* Psychotherapy and Psychosomatics. 2015;84(6):340–347.

Moncrieff J. *Antidepressants and the durability of treatment effects.* BMJ. 2015;350:h1438.

Zimmerman M, Chelminski I, Posternak MA. *Generalizability of antidepressant efficacy trials.* American Journal of Psychiatry. 2005;162:1370–1372.

Kirsch I, Huedo-Medina TB, Pigott HE, Johnson BT. *Do outcomes of clinical trials resemble those of "real world" patients? A reanalysis of the STAR*D dataset.* Psychology of Consciousness: Theory, Research and Practice. 2018.

Gibbons RD, Hur K, Brown CH, Davis JM, Mann JJ. *Benefits from antidepressants: synthesis of 6-week patient-level outcomes from double-blind placebo-controlled randomized trials of fluoxetine and venlafaxine.* Archives of General Psychiatry. 2012;69(6):572–579.

Rutherford BR, Sneed JR, Roose SP. *Does study design influence outcome?* Psychotherapy and Psychosomatics. 2009;78:172–181.

Ronalds C, Creed F, Stone K, Webb S, Tomenson B. *Outcome of anxiety and depressive disorders in primary care.* British Journal of Psychiatry. 1997;171:427–433.

Dewa CS, Hoch JS, Lin E, Paterson M, Goering P. *Pattern of antidepressant use and duration of depression-related absence from work.* British Journal of Psychiatry. 2003;183:507–513.

Brugha TS, Bebbington PE, MacCarthy B, Sturt E, Wykes T. *Antidepressants may not assist recovery in practice.* Acta Psychiatrica Scandinavica. 1992;86(1):5–11.

Adverse effects

Read J, Williams J. *Adverse emotional effects of antidepressants: a systematic review.* International Journal of Risk & Safety in Medicine. 2018;29(3–4):1–18.

Montejo AL, Llorca G, Izquierdo JA, Rico-Villademoros F. *Incidence of sexual dysfunction associated with antidepressant agents.* Journal of Clinical Psychiatry. 2001;62(Suppl 3):10–21.

Read J, Cartwright C, Gibson K. *Adverse emotional and interpersonal effects reported by 1829 New Zealanders while taking antidepressants.* Psychiatry Research. 2014;216(1):67–73.

Price J, Cole V, Goodwin GM. *Emotional side-effects of selective serotonin reuptake inhibitors: qualitative study.* British Journal of Psychiatry. 2009;195(3):211–217.

Healy D, Whitaker C. *Antidepressants and suicide: risk–benefit reconsidered.* BMJ. 2003;327:968–971.

US Food and Drug Administration. *Suicidality in children and adolescents being treated with antidepressant medications.* Public Health Advisory. 2004.

Stone MB, et al. *Risk of suicidality in clinical trials of antidepressants in adults.* BMJ. 2009;339:b2880.

Sharma T, Guski LS, Freund N, Gøtzsche PC. *Suicidality and aggression during antidepressant treatment: systematic review and meta-analyses.* BMJ. 2016;352:i65.

Leo RJ. *Movement disorders associated with SSRIs.* Journal of Clinical Psychiatry. 1996;57(10):449–454.

Withdrawal

Fava GA, Gatti A, Belaise C, Guidi J, Offidani E. *Withdrawal symptoms after antidepressant discontinuation: a systematic review.* Psychotherapy and Psychosomatics. 2015;84(2):72–81.

Davies J, Read J. *A systematic review into the incidence, severity and duration of antidepressant withdrawal effects.* Addictive Behaviors. 2019;97:111–121.

Horowitz MA, Taylor D. *Tapering of SSRI treatment to mitigate withdrawal symptoms.* The Lancet Psychiatry. 2019;6(6):538–546.

Horowitz MA, Taylor D. *Distinguishing relapse from withdrawal during antidepressant discontinuation.* The Lancet Psychiatry. 2020;7(6):465–467.

Stockmann T, Odegbaro D, Timimi S, Moncrieff J. *SSRI and SNRI withdrawal symptoms reported on an internet forum.* International Journal of Risk & Safety in Medicine. 2018.

Read J. *How common and severe are six withdrawal effects from, and addiction to, antidepressants?* Addictive Behaviors. 2020;102:106157.

Maintenance and relapse prevention

Geddes JR, Carney SM, Davies C, et al. *Relapse prevention with antidepressant drug treatment in depressive disorders.* The Lancet. 2003;361(9358):653–661.

Andrews PW, Kornstein SG, Halberstadt LJ, Gardner CO, Neale MC. *Blue again: perturbational effects of antidepressants suggest monoaminergic homeostasis in major depression.* Frontiers in Psychology. 2011;2:159.

Glue P, Donovan MR, Kolluri S, Emir B. *Meta-analysis of relapse prevention antidepressant trials: enrichment and withdrawal effects.* Journal of Affective Disorders. 2010;123(1–3):9–16.

Implications

General Medical Council. *Decision making and consent.* GMC guidance.