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Dose-response effects of selective serotonin reuptake inhibitor monotherapy for the treatment of depression: systematic review of reviews and meta-narrative synthesis

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ABSTRACT

OBJECTIVE To assess and clarify the relations between selective serotonin reuptake inhibitor (SSRI) dose efficacy, acceptability (early treatment discontinuation (dropouts)), and tolerability (reported adverse drug effects), and critically evaluate methods previously used to examine SSRI dose-response effects for the treatment of depression in adults.

DESIGN Systematic review of reviews and meta-narrative synthesis.

DATA SOURCES Embase, Medline, PsycINFO, Scopus, and the Cochrane Collaboration library, from 1975 to December 2021. Reference lists of national depression treatment guidelines were systemically searched by hand.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES Reviews assessing SSRI monotherapy dose-response effects for the treatment of depression in adults (age ≥18 years) reporting efficacy, acceptability, or tolerability. Reviews meeting inclusion criteria had a high degree of heterogeneity, due to methodological diversity; therefore, a meta-narrative synthesis approach was applied. Standard daily doses were defined as 20 mg citalopram, fluoxetine, paroxetine; 50 mg sertraline; and 10 mg escitalopram. Risk of bias was assessed using the Risk of Bias in Systematic Reviews tool, in line with Cochrane recommendations.

RESULTS The search identified 9138 records; 387 full text reports were assessed for eligibility, 42 of which matched the inclusion criteria. The majority, 83% (n=35), of reviews included data for studies with a duration of ≤12 weeks (ie, the acute phase of depression treatment). Of 39 reviews assessing efficacy, the majority (n=26) indicated that individual SSRIs and SSRI class demonstrated flat dose-response effects; standard doses were optimal for efficacy. Acceptability or tolerability were assessed in 28 reviews. Higher than standard daily doses were associated with higher dropout rates and a greater incidence of adverse drug effects (eg, nausea, sexual dysfunction, fatigue, anxiety). Despite a range of methods being reported, there was an overall consensus regarding SSRI dose related efficacy, dropouts, and adverse drug effects.

CONCLUSION Standard daily doses of SSRIs for the treatment of depression in adults provide a favourable balance between efficacy, acceptability, and tolerability. Patients are encouraged to talk to their prescriber or community pharmacist if they experience adverse effects or have any concerns about their drug treatments.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed antidepressants for depression treatment worldwide
⇒ In recent years, higher doses of SSRIs are being used to treat depression
⇒ It is unclear whether SSRIs show a dose-response effect for efficacy in depression treatment, and most clinical guidelines lack clarity regarding antidepressant dose-response effects
⇒ Use of higher SSRI doses could expose people to avoidable drug related harms without providing greater efficacy

WHAT THIS STUDY ADDS

⇒ Standard daily doses (20 mg citalopram, fluoxetine, paroxetine; 50 mg sertraline; and 10 mg escitalopram) provide a favourable balance between efficacy, acceptability, and tolerability, in the acute phase of treatment
⇒ Higher than standard daily doses were associated with higher dropout rates and a greater incidence of adverse drug effects (eg, nausea, sexual dysfunction, fatigue, anxiety)

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ There is a lack of primary studies assessing the dose-response effects in older adults who are commonly prescribed SSRIs
⇒ Routinely increasing SSRI doses for individuals not achieving satisfactory symptom resolution or remission does not appear to be supported by current evidence
⇒ Prescribers might find these findings of use when discussing antidepressant dose limitations and harms with patients
⇒ Clearer inclusion of antidepressant dose-response effects and efficacy limitations in clinical guidelines could help to better optimise outcomes while minimising avoidable drug related harms

Introduction

Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed antidepressants around the world, accounting for more than 50% of all antidepressant prescriptions.[1–4] Most SSRIs are prescribed for the treatment of depression.[5 6] Over recent years, use of higher than standard licensed SSRI doses for depression treatment has increased in UK primary care and elsewhere.[5 7–9]

SSRIs exert their effects via serotonin reuptake inhibition, and have a hyperbolic association between dose, transporter occupancy, and plasma concentration with SSRI doses of 20 mg citalopram, fluoxetine, paroxetine; 50 mg sertraline; and

10 mg escitalopram; with daily doses providing optimal receptor occupancy and serotonin effects.[10] Therefore, the theoretical rationale for increasing standard daily doses of SSRIs for individuals not achieving satisfactory symptom resolution or remission are scarce. Conversely, tricyclic antidepressants and serotonin and noradrenaline (norepinephrine) reuptake inhibitors (SNRIs) have shown serotonin, norepinephrine, and dopamine effects as doses are increased.[11 12] For example, venlafaxine shows predominantly serotonin effects at doses <150 mg per day, with norepinephrine effects becoming clinically significant from ≥150-225 mg per day, and dopamine reuptake inhibition from >225 mg per day.[12] Therefore, tricylic antidepressants and SNRIs demonstrate dose-response effects for efficacy owing to their multiple receptor effects with higher doses being more effective where they are tolerated.[13 14]

Over the past 20 years numerous reviews have assessed antidepressant efficacy,[15 16 17] however, few have assessed dose-response effects. These reviews have shown a mixed picture—some have indicated that higher than standard initiating doses are more efficacious,[18 19] while others have refuted this finding,[13 20] demonstrated mixed effects,[21] or remained ambiguous.[22] In part, some of these differences in findings might be due to newer analytical methods being more comprehensive and robust; but newer reviews also show mixed findings.[18–20 23] However, some reviews agree that higher doses are associated with more adverse drug effects.[13 19 21–23]

This ambiguity regarding SSRI dose-response and efficacy feeds into national guidelines for depression treatment in Europe, North America, and Australasia, where few highlight the possible limitations of increasing SSRI doses,[24 25] and lack clarity (see online supplemental table S1).[26 27 28] Clinicians might therefore decide to increase SSRI doses routinely, and while in part this increase could be due to the doses used in clinical trials and different prescribing cultures (ie, higher SSRI doses more commonly prescribed in North American trials compared with European studies[29 30]), it might also be in response to some patients' expectations of higher doses being more effective.[31] However, whether increasing SSRIs doses provides greater efficacy for the treatment of depression remains unclear. Therefore, this systematic literature review of reviews aimed to assess and clarify the relation between SSRI dose for efficacy (response and/or remission), acceptability (early treatment discontinuation—dropouts) and tolerability (reported adverse drug effects), and critically evaluate the methods previously used to examine SSRI dose-response effects for the treatment of depression in adults.

Methods

Study design

Recommendations from the Cochrane Handbook for Systematic Reviews of Interventions informed the design of this systematic review.[32] This systematic review was conducted according to the PRISMA (preferred reporting items for systematic reviews and meta-analyses) 2020 checklist.[33] The publicly available protocol for this review of reviews is available on the institutional website of University of Stirling (http://hdl.handle.net/1893/33209). Previous reviews have applied a diverse range of review methodologies to assess SSRI dose-response effects; therefore, we applied a meta-narrative synthesis approach for this review of reviews.

This systematic meta-narrative synthesis is reported in compliance with PRISMA and RAMESES (realist and meta-narrative evidence syntheses: evolving standards).[33 34] The updated PRISMA flow chart was used to outline study selection process used to identify reviews which met the inclusion criteria.[33] A meta-narrative review is a method of systematic review, designed for topics that have been conceptualised differently and studied by different groups of researchers. A meta-narrative synthesis brings together the studies that have been differently conceptualised by different researchers.[34]

Search strategy and criteria of eligibility and inclusion

The inclusion criteria for this systematic review and synthesis are presented according to PICOS (population, intervention, comparator, outcomes, study design) criteria (table 1).

Population

We included literature reviews for adults aged ≥18 years with depression. Depression was used as

Table 1 | PICOS inclusion criteria

PICOS category	Inclusion criteria
Population	▶ Adults aged ≥18 years ▶ Major depressive disorder
Intervention	▶ Monotherapy ▶ Selective serotonin reuptake inhibitors: escitalopram, citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline
Comparison	▶ Placebo ▶ Selective serotonin reuptake inhibitors
Outcomes	▶ Antidepressant response ▶ Efficacy: reduction in depression signs and symptoms ▶ Acceptability: early treatment discontinuation ▶ Tolerability: any reported adverse drug effects
Study design	▶ Dose-response ▶ Review ▶ Narrative review ▶ Systematic review ▶ Meta-analysis ▶ Meta-regression ▶ Network meta-analysis

PICOS = population, intervention, comparator, outcomes, study design.

the common summary term that included: major depressive disorder, unipolar depression, depressive disorder, endogenous depression, and organic depression. Diagnostic criteria and severity of depression were not defined because primary studies were not being assessed. We considered a broad age range appropriate owing to the common trend of ageing populations across westernised societies, and about 20% of older adults (aged ≥65 years) receiving antidepressants in the UK and US.[1 4 35]

We excluded reviews of children and adolescents aged <18 years with depression, because this cohort is not routinely treated in primary care by general practitioners and have variable response rates to antidepressants.[36] Reviews including older people with dementia were excluded because antidepressants have questionable benefits for depressive symptoms in this cohort.[37] Additionally, owing to differences in disorder causes, bidirectional effects between depression and comorbidities, and previous evidence of treatment resistance, we excluded the following criteria: treatment resistant depression, depression during pregnancy, perinatal depression, postnatal depression, bipolar disorder, concomitant psychiatric disorders, people who use drugs, concomitant opioid replacement treatment, or specific comorbidities (eg, diabetes, post-myocardial infarction).[38–41]

Interventions and comparators

Reviews assessing SSRI monotherapy for the treatment of depression for all licensed SSRIs were included: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline. The SSRI zimelidine was not included because it has been withdrawn from the market, owing to its use being associated with Guillain-Barré syndrome.[42] Antidepressants outside the SSRI class with novel serotonin or mixed receptor effects were excluded: vortioxetine is a direct modulator of serotonergic receptor activity and inhibitor of serotonin reuptake; vilazodone has mixed SSRI and buspirone-like activity; the SNRIs venlafaxine and duloxetine; the tricyclic antidepressant clomipramine; and bupropion and agomelatine.[43–45]

Reviews examining combination treatments (using two or more antidepressants; psychotropic and non-psychotropic medicine augmentation strategies; antidepressant with psychotherapies; and switching antidepressants) were excluded because these strategies can be more effective than monotherapy and can be reserved for treatment resistant depression.[24–28] Most national guidelines[24–28] and drug licenses recommend standard starting doses,[43] which are routinely prescribed in practice,[5 9 46 47] and represent standardised defined daily doses as defined by the World Health Organization.[48] It was therefore considered appropriate to assess baseline standardised comparator dose effects against placebo and higher SSRI doses, but owing to the range of methodologies and reporting methods, it was not possible to summarise the magnitude of effects using defined daily doses.

Outcomes

These outcomes were defined as dose-response effects for efficacy, acceptability, tolerability. Efficacy was defined as a response to antidepressant treatment, which is routinely defined as a ≥50% reduction in observer rated depression severity rating scales such as the Hamilton depression rating scale, Montgomery-Åsberg depression rating scale, or Beck depression inventory,[26] or remission. Acceptability was defined as early treatment discontinuation (dropout) or non-completion of the study. Tolerability was defined as patients experiencing reported adverse drug effects including death, suicidality, and effects relating to major organ systems (cardiovascular system (eg, arrhythmias, QTc prolongation); central nervous system (eg, headache, anxiety, insomnia, hypersomnia); dermatological; endocrine system; ear; eye; gastrointestinal; genital urinary and reproductive; haematological; musculoskeletal; respiratory; and other non-categorical adverse drug effects).

Review design and setting

Reviews assessing dose-response effects for oral SSRI use in human adults for the treatment of moderate to severe depression were included. Data from the following study designs were included: pooled data, systematic literature, narrative, meta-analysis, meta-regression, or network meta-analysis. Data from primary and secondary care were included—although currently most antidepressants are prescribed in primary care to treat depression, a large proportion of the initial randomised controlled trials that inform current practice were based in secondary care inpatient or outpatient settings, not general practice. The duration of treatment was not defined in order to capture information regarding short and long term use and potential dose-response effects at different periods of depression treatment.

Information sources and literature search

We searched Embase, Medline, PsycINFO, Scopus, and Cochrane Collaboration library electronic databases. Reference lists of national and international depression treatment guidelines were searched by hand to identify previous reviews.[24–28] Reference lists of editorials, commentaries, and letters identified from the electronic database searches were also searched for previous reviews. We searched for reviews or meta-analysis for all licensed SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) as monotherapy for the treatment of major depressive disorder. Key

search terms included "systematic review," "meta-analysis," "dose-response relationship," "dose-response," "antidepressant$," "antidepressive agent$," "citalopram," "escitalopram," "fluoxetine," "fluvoxamine," "paroxetine," "sertraline," "serotonin uptake inhibitor$," "serotonin reuptake inhibitor$," "SSRI," "depression," "depressive disorder," "depressive disorder major," "unipolar depression," "major depressive disorder," and "human" (online supplemental file 1).

Studies on fluoxetine were first published in the mid-1970s; the SSRI that has been available on the market for the longest period.[49] Therefore, 1975 was used as the start date until the end of December 2021. Reviews were limited to English language.

Literature inclusion process and data extraction

Article titles and abstracts were screened for inclusion. Subsequently, potentially relevant full text articles from the literature search were then screened for inclusion by a structured process and standard terms supporting inclusion and exclusion. Studies that did not meet the criteria outlined above were excluded.

We extracted the following data for each review article using a standardised data collection form specifically designed and tested for this systematic review: review characteristics (eg, lead author, type of review, protocol driven review, patient level data or not, type of depression being treated, review setting in primary or secondary care), antidepressant and comparator information (eg, SSRI used, fixed or flexible dose study, placebo controlled, dose standardisation technique, treatment duration), and dose-response effects (eg, efficacy, dropouts, and adverse drug effects).

Risk-of-bias assessment

Each review article was assessed according to the ROBIS (risk of bias in systematic reviews) tool,[50] in line with Cochrane recommendations.[32] Reviews were assessed by CFJ using ROBIS and checked by SM. The ROBIS tool has been specifically developed and designed to assess reviews within healthcare settings, and has three phases: assessment of relevance, identification of concerns with the review process, and judgment of risk of bias. The second phase covers four domains: study eligibility criteria, identification and selection of studies, data collection and study appraisal, and synthesis of findings. The third phase assesses overall risk of bias (low, high, unclear) from interpretation of review findings, and considers limitations identified in any of the domains in the second phase.[50]

No consensus exists on how best to assess and deal with overlap (ie, duplication), where primary studies are included more than once across two or more reviews that might bias findings; although a range of methods have been applied (such as only including meta-analysis or reviews assessed as being at low risk of bias), these could lead to loss of information.[51–53] In order to avoid loss of information, and to demonstrate the diversity of reviews that met inclusion criteria, we conducted a sub analysis assessing the corrected covered area (CCA) for reviews assessed as being at low risk of bias. A citation matrix and pairwise CCA were calculated and tabulated according to Cochrane guidance.[53 54] Grading was applied, as previously defined by Pieper et al.[53] Similarly, no consensus exists regarding sensitivity analysis and how best assess sensitivity of findings; therefore, findings from the CCA analysis were analysed to identify discordant review findings and assess differences.[52]

No consensus exists on how best to assess and present data on the quality of primary studies.[52] Therefore, for reviews assessed as being at lower risk of bias, we determined the methodological quality of the primary studies using the review authors' original assessment of risk of bias by domains. Primary studies were classified as having low risk of bias if none of the domains was rated as high risk of bias and three or less were rated as unclear risk; they were classified as having moderate risk of bias if one or none was rated as high risk of bias but four or more were rated as unclear risk; and all other cases were assumed to relate to a high risk of bias.[55] We then identified overall primary study quality, across the reviews at low risk of bias, by applying the most frequent quality assessment rating (eg, for three reviews rating a primary study as high, high, and low risk of bias, the study was recorded as high); for primary studies included in two reviews that did not agree on rating, the lower assessment rating was applied (eg, with a high and moderate risk of bias, the study was recorded as high).

Data analysis, synthesis, and ethics

In view of the heterogeneity of primary reviews, owing mainly to methodological diversity (ie, narrative, meta-analysis, network meta-analysis, meta-regression), it was considered appropriate to apply a meta-narrative synthesis approach.[34] Tables were used to summarise the population, interventions, and outcomes of interest.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research, owing to the lack of resources to enable such involvement.

Results

Dose-response effects of selective serotonin reuptake inhibitors

A total of 9138 records were identified from electronic search, hand searching reference lists, and grey literature. We assessed 387 full text reports for eligibility, and 42 reviews based on published and

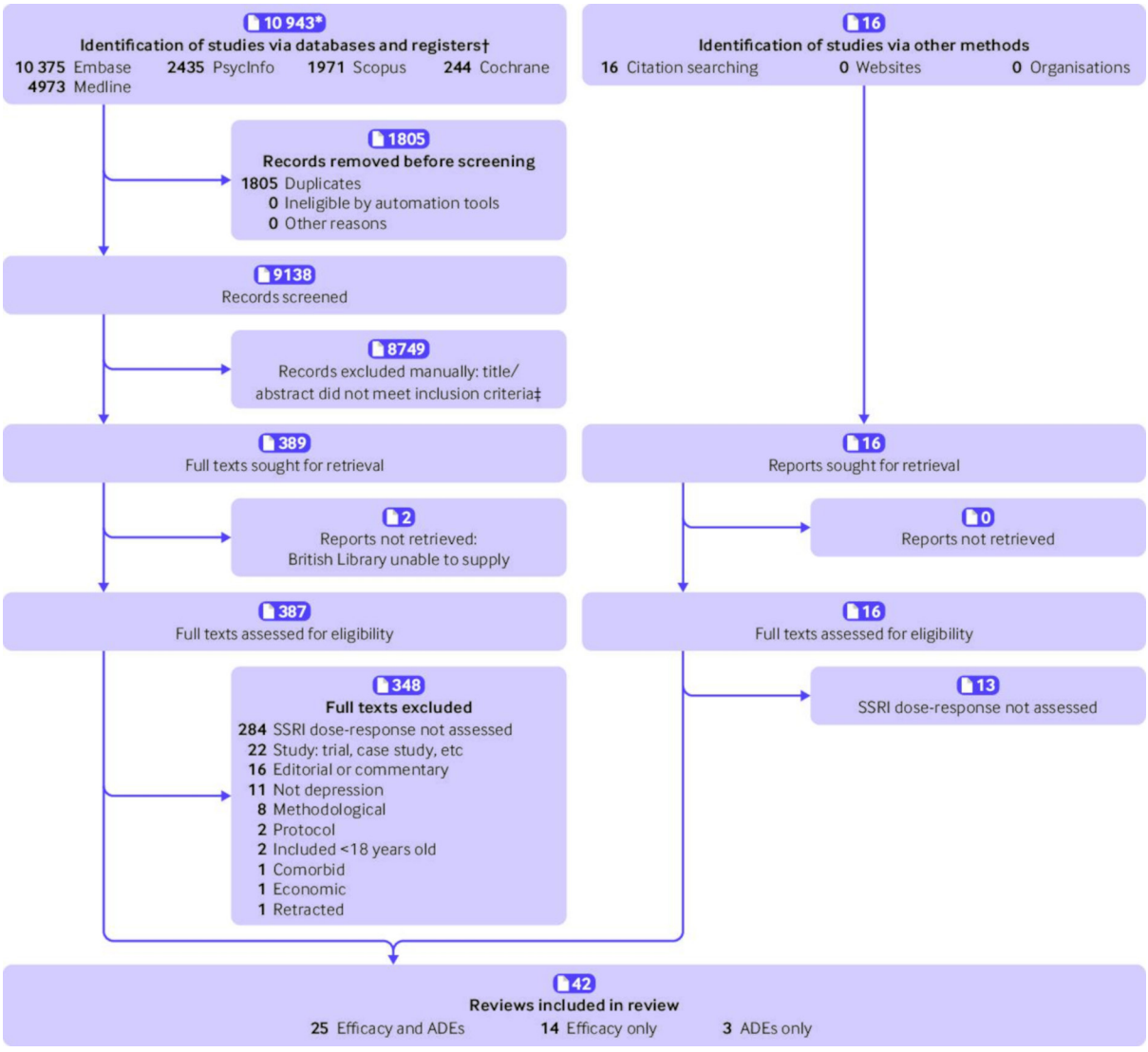

Figure 1 | Review identification, inclusion, and exclusion. *Total records identified include combined records from Embase, Medline, and PsychInfo (n=8728), plus those from Scopus and Cochrane. †Number of records listed are those identified from each database (rather than the total number across all databases). ‡No automated tools used, as per PRISMA 2020 guideline. SSRI=selective serotonin reuptake inhibitors; ADE=adverse drug effect

unpublished reviews matched the inclusion criteria: 25 assessed SSRI efficacy, adverse drug effects, and dropouts; 14 assessed SSRI efficacy only; and three assessed adverse drugs effects and dropouts only (figure 1). The year of publication ranged from 1988 to 2021. A range of review methods were used: 60% (n=25) were meta-analyses (14 systematic reviews, seven non-systematic reviews, and four reviews using pooled study data) and 40% (n=17) were narrative reviews (including three that reported to have systematically identified primary studies, and eight that had included a mix of primary and secondary studies (meta-analysis and/or narrative reviews); table 2 and online supplemental table S2).

Of the 42 reviews identified, 83% (n=35) included data from studies for 12 weeks or less (the acute phase of depression treatment), whereas five did not define the treatment period and two lacked greater detail. Four reviews considered the continuation phase and relapse prevention, but did not report on dose-response effects during the continuation phase.[56–59] The care setting also varied; 17% (n=7) of reviews reported to have included data from studies conducted in primary care (general practice or outpatient clinics), 26% (n=11) included data from studies conducted in both primary and secondary care, whereas 57% (n=24) did not define the care setting.

Efficacy

The majority of reviews, 93% (n=39), assessed SSRI dose-response effects for the treatment of depression (table 2). Most reviews (n=26) indicated that the SSRI class of antidepressant demonstrated flat dose-response effects for the acute phase of treatment of depression; higher than standard daily doses did not provide greater efficacy.[13 20 56 57 59–80] A minority

Table 2 | Efficacy, dropouts (acceptability), and adverse effects (tolerability) of eligible reviews investigating dose-response effects of selective serotonin reuptake inhibitor monotherapy for the treatment of depression

Review author and year	No of primary studies	Review design	Efficacy and dose*	Dropouts and adverse drug effects*	Dose standardisation	Study duration (range)	Risk of bias in review
Braun 2020[60]	33	SR MA, network MA	↔ SSRI grouped ↔ citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline	↑ SSRI grouped	Low, medium, high	6 (2-12) weeks	Low
Cheng 2020[61]	115	Model based MA	↔ citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline	NA	Fluoxetine dose equivalents	4-12 weeks	Low
Dold 2017[62]	5	SR MA, MR	↔ fluoxetine, paroxetine, sertraline	↑ fluoxetine	Fluoxetine 20 mg/day, paroxetine 20 mg/day, and sertraline 50 mg/day *v* higher doses	5 (3-8) weeks	Low
Furukawa 2019[23]	66	SR MA	↑ SSRI grouped (to 40 mg/day) ↑ citalopram (to 30 mg/day); ↔ escitalopram, fluoxetine, paroxetine; ∩ sertraline	↑	Fluoxetine dose equivalents	8 (4-12) weeks	Low
Furukawa 2020[63]	108	SR MA	↔ SSRI grouped ↔ citalopram, escitalopram, fluoxetine, paroxetine, sertraline	↑ flexible dose	Fluoxetine dose equivalents	7 (4-12) weeks	Low
Benkert 1996[64]	7 (+7 reviews)	Narrative review	↔ citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline	NA	Actual doses from other reviews	Not defined	Unclear
Dunner 1992[56]	Pooled (n=460)	Pooled SKB data	↔ paroxetine	NA	Paroxetine dose	Acute phase ≤6 weeks; long term phase 52 weeks	Unclear
Gutsmiedl 2020[65]	44	SR MA, MR	↔ SSRIs and non-SSRIs grouped	NA	Fluoxetine dose equivalents	9 (4-26) weeks	Unclear
Hamza 2021[81]	60	MA	SSRI grouped (↑ to 40 mg/day), ↑ citalopram (to 30 mg/day), paroxetine (to 40mg/day), sertraline (to 75 mg/day), ↔ escitalopram, fluoxetine	NA	Fluoxetine dose equivalents: individual drug effects reported as fluoxetine dose equivalents and not actual drug doses	8 (4-12) weeks	Unclear
Khan 2003[66]	36	FDA submissions, MA	↔ SSRIs and non-SSRIs grouped	↑	SSRI study doses used	6-8 weeks	Unclear
Klemp 2011[67]	26	SR, MR	↔ paroxetine	NA	Paroxetine dose	8 (6-56) weeks	Unclear
Montgomery 1995[57]	1	Narrative review	↔ sertraline	↑	Sertraline dose	Acute phase 6-8 weeks; long term phase 44 weeks	Unclear
Murdoch 2005[88]	Pooled (n=1307)	Pooled Lundbeck Forrest data	NA	↑ escitalopram	Escitalopram dose	Not defined	Unclear
Preskorn 1995[68]	3	Narrative review	↔ sertraline	↑	Sertraline dose	≤8 weeks	Unclear
Purgato 2015[69]	173	SR, MR	↔ fluoxetine	NA	Mean doses poorly reported. Minimum and maximum doses (mg), expressed as multiples of defined daily doses. Prescribed study doses were then divided by define daily doses and grouped as ≤20 or 20-80 mg/day	Majority ≤6 weeks	Unclear
Safer 2016[20]	33	Narrative review	↔ SSRIs and non-SSRIs grouped ↔ citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline	↑	SSRI dose	8-28 weeks	Unclear
Tan 1999[58]	2 (+1 reviews)	Narrative review	? citalopram	↑	Citalopram dose	6 (3-24) weeks	Unclear
Vaswani 2003[70]	3 (+5 reviews)	Narrative review	↑ citalopram (to 40 mg/day) ↔ fluoxetine, fluvoxamine, paroxetine, sertraline	↑	Not defined	Not defined	Unclear
Adli 2005[13]	12	SR, narrative review	↑ fluvoxamine ↔ citalopram, fluoxetine, paroxetine, sertraline	↑	SSRI dose	4-8 weeks	High
Altamura 1988[71]	2	Narrative review	↔ fluoxetine	↑	Fluoxetine dose	6 weeks	High
Baker 2003[22]	4	SR MA	? fluoxetine, paroxetine, sertraline	↑	Low, medium, high. No clear definition	≤8 weeks	High
Barbui 2002[82]	103	SR MA	↑ fluoxetine	↑	20-30, >30 mg/day; dose range 20-40 and >40 mg/day	≤9 weeks	High
Beasley 1990[72]	Pooled (n=669)	Pooled	↔ fluoxetine	↑	Fluoxetine dose	≤8 weeks	High
Beasley 1993[89]	3	Narrative review	NA	Fluoxetine: ↑ anxiety, agitation, insomnia, drowsiness, asthenia	Not defined	6 weeks	High
Berney 2005[73]	14 (+4 reviews)	Narrative review	↔ citalopram, escitalopram, fluoxetine, paroxetine, sertraline ? fluvoxamine	↑ fluoxetine, sertraline	SSRI dose	6-8 weeks	High
Bollini 1999[21]	33	SR MA	∩ SSRIs and non-SSRIs grouped	↑	Imipramine dose equivalents	6 (4-24) weeks	High
Caley 2002[86]	5 (+7 reviews)	Narrative review	↑ citalopram; ∩ fluvoxamine; ↔ fluoxetine, sertraline; ? paroxetine	↑	SSRI dose	4-6 weeks	High

Continued

Table 2 Continued

Review author and year	No of primary studies	Review design	Efficacy and dose*	Dropouts and adverse drug effects*	Dose standardisation	Study duration (range)	Risk of bias in review
Corruble 2000[74]	10 (+6 reviews)	SR, narrative review	↔ SSRI grouped	NA	SSRI dose	4-8 weeks	High
Hansen 2009[83]	74	SR MA, MR	↑ SSRIs and non-SSRIs grouped	NA	Licensed dose range (eg, fluoxetine: low <45 mg/day, high >45 mg/day)	7 (6-24) weeks	High
Hieronymus 2016[18]	11	MA, industry data	↑ citalopram, paroxetine, sertraline	NA	Patient level doses	≤6 weeks	High
Holper 2020[87]	153	Network MA	↑ escitalopram, fluoxetine ↔ citalopram, paroxetine	↑ (age ≤70 years); ↑↑ (age >70 years)	Fluoxetine dose equivalents	4-12 weeks	High
Jakubovski 2016[19]	40	SR MA	↑ SSRIs grouped	↑	Imipramine dose equivalents	6 (4-24) weeks	High
Jenner 1992[75]	Pooled (n=4668)	Pooled SKB data	↔ paroxetine	↑	Paroxetine dose	6 weeks (≤2 year)	High
Lam 2006[76]	3	MA of Lundbeck data	↔ escitalopram	NA	Escitalopram dose	8 weeks	High
Lane 1995[77]	4 (+2 reviews)	Narrative review	↔ citalopram, fluoxetine, paroxetine, sertraline	↑	Not defined	Not defined	High
Montgomery 1994[78]	9	MA	↔ citalopram	NA	Citalopram dose	4-6 weeks	High
Montgomery 1995[59]	2 (+2 reviews)	Narrative review	↔ citalopram	NA	Citalopram dose	≤24 weeks	High
Oliva[90]	Not defined	SR MA	NA	↑ nausea and vomiting, citalopram, escitalopram	Low *v* high dose	6-12 weeks	High
Papakostas 2010[84]	9	SR MA	↑ SSRIs grouped	↑	Usual (10 mg/day: escitalopram, citalopram; 20 mg/day: fluoxetine, paroxetine, sertraline; 50 mg/day: fluvoxamine), intermediate, double usual dose, and higher	6 weeks	High
Parker 2000[85]	1 (+1 review)	Narrative review	↑ citalopram	↑	Citalopram dose	4-6 weeks	High
Rifkin 1997[79]	4	Narrative review	↔ fluoxetine, paroxetine, sertraline	NA	SSRI dose	Not defined	High
Ruhe 2006[80]	8	SR, narrative review	↔ fluoxetine, paroxetine, sertraline	↑	SSRI dose	8 (3-12) weeks	High

Reviews in this table are ranked by assessed risk of bias (last column), and then alphabetically by author (first column). SSRI=selective serotonin reuptake inhibitor; SR=systematic review; MA=meta-analysis; MR=meta-regression; SKB=SmithKline Beecham; FDA=federal drug agency; NA=not assessed; acute=acute phase of depression treatment; long term=long term phase of depression treatment.

*Drug response effects are indicated as ↑ (increased), ↑↑ (marked increase), ↔ (flat), ∩ (curvy linear), or ? (unclear).

(n=8) demonstrated that higher doses were more efficacious,[18 19 23 81–85] while others (n=3) showed mixed effects,[21 86 87] or remained ambiguous.[22 58]

At an individual SSRI level, most reviews also demonstrated flat dose-response effects for efficacy; standard daily starting doses were the optimal doses: 20 mg citalopram, 10 mg escitalopram, 20 mg fluoxetine, 20 mg paroxetine, and 50 mg sertraline (table 3).[13 20 23 56 57 59–64 67 68 70–73 75–80 82 86] A minority of reviews however, indicated that some SSRIs did have linear dose-response effects with higher doses being more effective, for example, escitalopram[87]; citalopram (eg, up to 30 mg/day[18 23 81 85 86]); fluoxetine[82 87]; fluvoxamine[13]; paroxetine[18 81]; and sertraline.[18] Other reviews indicated mixed curvy linear efficacy with increasing doses for fluvoxamine[86] and sertraline.[23 81] All curvy linear efficacy responses were characterised by having an initial increase, a peak, and and then a decline in efficacy with increasing dose.

Blood plasma concentrations of fluoxetine, fluvoxamine, and paroxetine were assessed in association with response rates to depression treatment. We found no correlation between blood plasma concentrations and individual responses to treatment, regardless of the severity of depression.[70 72]

Six reviews compared the efficacy of fixed daily doses with flexible dose regimens for individuals not achieving satisfactory symptom resolution or remission (two narrative reviews[73 80] and four meta-analyses[62 63 66 87]). All reviews demonstrated that use of flexible dose titration for these individuals did not provide greater efficacy.

Acceptability and tolerability

Of the 42 reviews, 28 (67%) assessed and reported the dose-response effects related to acceptability (early treatment discontinuation—dropouts) and tolerability (reported adverse drug effects). All reviews demonstrated that dropouts and adverse drug effects increased with increasing dose (table 2).

At a class and individual SSRI level, the following adverse drug effects were associated with (but not limited to) dose-response effects: nausea, sexual dysfunction, fatigue, anxiety, and insomnia.[13 20–23 57 58 60 63 68 70–73 75 77 82 85 86 88–90] A network meta-analysis identified escitalopram as potentially providing the optimal balance between

Table 3 | Efficacy dose-response effects by individual selective serotonin reuptake inhibitor*

Study	Design	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline	Risk of bias in review
Braun 2020[60]	SR MA	↔	↔	↔	↔	↔	↔	Low
Cheng 2020[61]	Model based MA	↔	↔	↔	↔	↔	↔	Low
Furukawa 2019[23]	SR MA	↑	↔	↔		↔	∩	Low
Furukawa 2020[63]	SR MA	↔	↔	↔		↔	↔	Low
Dold 2017[62]	SR MA			↔		↔	↔	Low
Benkert 1996[64]	Narrative review	↔		↔	↔	↔	↔	Unclear
Safer 2016[20]	Narrative review	↔	↔	↔	↔	↔	↔	Unclear
Hamza 2021[81]	MA	↑	↔	↔		↑	↑	Unclear
Vaswani 2003[70]	Narrative review	↑		↔	↔	↔	↔	Unclear
Tan 1999[58]	Narrative review	?						Unclear
Purgato 2015[69]	SR, MR			↔				Unclear
Dunner 1992[56]	Pooled					↔		Unclear
Klemp 2011[67]	SR, MR					↔		Unclear
Montgomery 1995[57]	Narrative review						↔	Unclear
Preskorn 1995[68]	Narrative review						↔	Unclear
Adli 2005[13]	Narrative review	↔		↔	↑	↔	↔	High
Berney 2005[73]	Narrative review	↔	↔	↔	?	↔	↔	High
Holper 2020[87]	Network MA	↔	↑	↑		↔		High
Lane 1995[77]	Narrative review	↔		↔		↔	↔	High
Montgomery 1994[78]	MA	↔						High
Montgomery 1995[59]	Narrative review	↔						High
Caley 2002[86]	Narrative review	↑		↔	∩	?	↔	High
Lam 2006[76]	MA		↔					High
Altamura 1988[71]	Narrative review			↔				High
Beasley 1990[72]	Pooled			↔				High
Rifkin 1997[79]	Narrative review			↔		↔	↔	High
Ruhe 2006[80]	SR, narrative review			↔		↔	↔	High
Jenner 1992[75]	Pooled						↔	High
Hieronymus 2016[18]	MA	↑				↑	↑	High
Barbui 2002[82]	SR MA			↑				High
Parker 2000[85]	Narrative review	↑						High
Baker 2003[22]	SR MA			?		?	?	High

Reviews in this table are are ranked by assessed risk of bias (low to high), most common finding for efficacy, and dose-response effect; selective serotonin reuptake inhibitors ordered alphabetically.
MA=meta-analysis; MR=meta-regression; SR=systematic review

*Drug response effects are indicated as ↑ (increased), ↔ (flat), ∩ (curvy linear), or ? (unclear).

efficacy and tolerability.[87] However, this study considered that escitalopram doses up to 27 mg/day might be more effective, and all SSRIs demonstrated a poor risk-benefit ratio for older adults (age >70 years old) owing to adverse effects exceeding potential efficacy.

In the six reviews comparing flexible upward dose titration with maintenance dose for individuals not achieving satisfactory symptom resolution or remission, researchers also demonstrated that higher doses were associated with poorer acceptability and tolerability.[62 63 66 73 80 87]

Risk of bias

The assessment revealed that the minority (12%, n=5) of reviews were at low risk of bias (table 2, figure 2 and online supplemental table S3).[23 60–63] Four reviews demonstrated a flat dose-response effect for efficacy, and a positive dose-response effect for adverse drug effects and dropouts for all SSRIs.[60–63] One review, however, indicated that citalopram demonstrated efficacy dose-response to 30 mg/day, and sertraline showed curvy-linear effects peaking at about 75 mg/day.[23] Thirteen (31%) reviews were assessed as having an unclear risk of bias, whereas the majority (57%) had a high risk of bias that was mainly associated with a range of methodological issues.

Overlap assessment of primary studies across the five reviews at low risk of bias was very high, with a CCA of 26%.[23 60–63] Pairwise overlap assessment indicated that one review demonstrated slight overlap (≤5%), whereas the reviews by Cheng et al 2020 and Furukawa et al 2019 and 2020 demonstrated high to very high overlap (figure 3). However, Furukawa et al (2019)[23] found that the optimal daily dose ranged between 20 mg and 40 mg fluoxetine equivalents, and citalopram up to 30 mg daily, which was at odds with the majority of reviews showing that 20 mg fluoxetine equivalents were optimal doses at a class and individual drug level.[60–63]

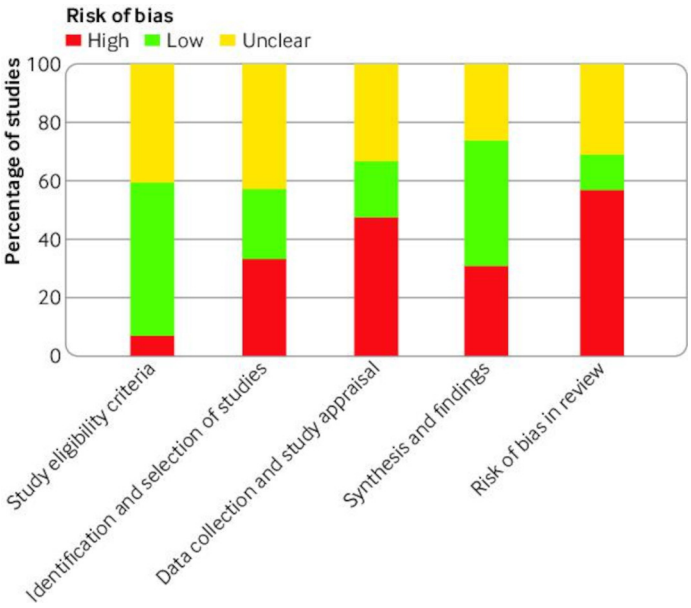

Figure 2 | ROBIS (risk of bias in systematic reviews) assessment of all 42 reviews meeting inclusion criteria. First four columns relate to judgments; last column relates to overall rating for risk of bias

Finally, of the 160 primary studies included in the five reviews, overall risk of bias was rated as low in 34 (21%) studies, moderate in 120 (75%), and high in six (4%) (online supplemental table S4). The majority of primary studies include participants aged ≥18 to ≤65 years, with an average age of about 40 years. Six (4%) primary studies assessed antidepressant effects for older adults (age >65 years), limiting the assessment of dose-response effects for this population. Eleven (7%) of the primary studies were identified as inlcuding patients with mild depression as defined in current guidelines (eg, Hamilton Depression 17 rating scale score <17).[26] However, after exclusion of the reviews that included people with mild depression,[23 60 61 63] lower doses continued to show non-inferiority to higher doses.[62]

	Braun 2020	Cheng 2020	Dold 2017	Furukawa 2019
Cheng 2020	11%			
Dold 2017	0%	0%		
Furukawa 2019	27%	35%	0%	
Furukawa 2020	16%	59%	0%	45%

Figure 3 | Corrected covered area pairwise matrix of primary studies citations.[23 60–63] Pairwise analysis of review citations assessed as being at low risk of bias. Overlap categorisation: slight (0-5%; white), moderate (6-10%), high (11-15%; yellow), very high (>15%; red)

Critical evaluation of previous reviews

Most reviews indicated that SSRIs had a flat dose-response effect for efficacy, and poorer acceptability and tolerability with higher doses for the treatment of depression. However, a range of methodological difficulties remain, which could explain some of the conflicting findings. Firstly, only a few reviews exclusively included or reported the effects of fixed dose studies,[13 20 22 23 57 66 68 71 73–75 79] while the majority included flexible dose studies. A weakness of reviews including flexible dose studies is that it requires clinicians to make a judgment early in treatment to increase the dose, which creates additional placebo effects that might be associated with the dose change, sometimes after several weeks of treatment.[80] This intervention could make drug response difficult or impossible to distinguish from spontaneous remission, because 50% of patients with clinical depression spontaneously remit within 12 weeks.[91] Furthermore, increasing doses could fit with patient's expectations regarding dose effects,[31] leading patients to receive higher than necessary doses, and potentially influencing the results of reviews using patient level data from flexible dose studies.[18 56 75] Flexible dose studies might also select dose tolerant patients who are able to complete these studies,[92] limiting generalisability and applicability to the wider population, and exposing patients to avoidable adverse drug effects. Newer reviews however, have compared the differences in effects between fixed and flexible dose studies, and report that no identifiable differences in efficacy between the groups, but that patients experience more adverse drug effects and dropouts with higher doses in both groups.[62 63 87]

Secondly, dose standardisation and drug grouping techniques (eg, imipramine dose equivalents and fluoxetine dose equivalents) standardise individual drugs from different classes with different doses, or dose ranges, against the tricyclic antidepressant imipramine or the SSRI fluoxetine.[19 21 23 61 63 65 81 84 87] Although standardisation might seem to have benefits, use of such grouping methods inadvertently oversimplifies antidepressant pharmacology, potentially missing differences between and within drug classes. It does not take account of, or even consider that, these grouping might be inappropriate. Unlike SSRIs that are highly specific for inhibiting serotonin transporter reuptake and increasing presynaptic serotonin levels, tricyclic antidepressants, SNRIs, and other non-SSRI antidepressants have mixed serotonin and non-serotonin (norepinephrine, dopamine, melatonin, muscarinic) effects that influence their dose-response efficacy and their adverse drug effect profiles.[10–12 14 93] Therefore, grouping drugs with different dose-response characteristics might provide questionable findings. Nonetheless, a few of these reviews have also

presented their findings for individual SSRIs that aid clarity and could help to better inform practitioners.[23 61 63 81 87]

Another difficulty with imipramine dose equivalents is that researchers have used irregular dose groupings: imipramine doses of <100, 100-199, 200-250, and >250 mg/day.[19 21] Introducing these groupings reduces sensitivity to detect dose-response differences, and gives greater weight to those patients that can tolerate higher doses. Imipramine dose equivalents are also based on arbitrary SSRI doses that cannot routinely be prescribed in clinical practice (eg, 45 mg citalopram, 125 mg sertraline, and 33.3 mg fluoxetine). However, other dose standardisation techniques have different limitations; for example, Braun et al compared non-equivalent low (potentially subtherapeutic) SSRI daily doses with standardised doses of the same compound (eg, ≤10 mg citalopram (equivalent to 5 mg escitalopram) *v* ≤9 mg escitalopram (equivalent to 18 mg citalopram)).[60] Citalopram is a racemic 50:50 mixture of active S-enantiomer (escitalopram) and inactive R-enantiomer, such that 2 mg of citalopram contains 1 mg of S-citalopram (escitalopram) and 1 mg of R-citalopram.[94–96] Conversely, Braun et al also categorised a wide range of doses as high in their study, which could have affected their findings—for example, ≥40 mg citalopram with ≥80 mg fluoxetine.[60] But other systematic reviews have focused on individual SSRIs, using the actual drug dose—therefore, removing interclass and intraclass variations.[13 18 20 56–59 61 67 71–76 78–80 85 86 88]

Few reviews focus on primary care (ie, general/family practice and outpatients).[67 68 71 72 83 89] While some reviews combine primary and secondary care inpatient studies,[23 59 63 65 69 73 75 76 81 82 86 87] most lack clarity regarding the study settings.[1318–2256–5860626466707477–8084858890]Therefore, the inclusion of inpatient studies could limit the generalisability of their findings to wider primary care populations, as demonstrated by Cheng et al.[61] Other methodological limitations include: inclusion of mild depression studies[23 61 63 74 81]; non-placebo controlled studies[22 23 81 82]; narrative reviews that might lack a systematic approach[20 57–59 64 68 70 71 73 77 79 80 85 86 88 89]; use of data on file, which misses search strategies and misses references, preventing others from replicating the review[56 66 75 76 81]; assessing and reporting on efficacy but not on adverse effects or dropout rates[18 20 56 59 61 64–67 69 74 76 78–81 83]; and assessing response without reporting remission effects. However, even after considering the potential limitations of previous reviews, this systematic review of reviews and meta-narrative synthesis shows an overall consensus that SSRIs demonstrate a flat dose-response effect for efficacy, and poorer acceptability and tolerability as SSRI doses are increased for the treatment of depression.

Discussion

Principal findings

Ambiguity regarding SSRI dose-response and optimal dosing for the treatment of depression has been a major challenge for prescribers, and for guideline developers in Europe, North America, and Australasia. This systematic review of reviews indicates that all individual SSRIs, except for fluvoxamine, demonstrate a ceiling effect for efficacy, and poorer acceptability and tolerability as SSRI doses were increased during the acute phase (up to 12 weeks) of depression treatment for adults. Dose-response efficacy, however, remains unclear for fluvoxamine.

The prescribing of higher than standard daily SSRI doses was associated with higher rates of early treatment discontinuation (poorer acceptability) and a higher incidence of adverse drug effects (poorer tolerability) such as, but not limited to, nausea, sexual dysfunction, anxiety, and insomnia. Comparison of fixed standard daily dose and flexible dose regimens for individuals not achieving satisfactory symptom resolution or remission demonstrated that dose titration above standard daily doses did not provide greater efficacy, but was associated with poorer acceptability and tolerability.

Strengths and weaknesses of the study

A major strength of this review was the inclusion and assessment of a range of meta-analyses and narrative reviews that met the inclusion criteria, and demonstrated the breadth and depth of review literature assessing SSRI dose-response effects. To our knowledge, this is the first review of reviews to investigate SSRI drug-response effects.

Although the literature search aimed to be as comprehensive as possible and included a range of reviews using different methodologies, it is possible, as with all systematic reviews, that an important review could have been missed. However, searching a range of key electronic databases and hand searching reference lists from guidelines and other sources helped to reduce the risk of missing relevant reviews. Inclusion of reviews in languages other than English could have been beneficial, but funding was not available for this inclusion. While inclusion of reviews only in the English language might be considered to limit generalisability of findings, the majority of reviews that were assessed as being at low risk of bias included non-English language primary studies, therefore overcoming language limitations.[23 60–63]

Other potential limitations were that data from individual published and unpublished randomised controlled studies might not have been included in the initial review. The reporting quality of many of the older reviews was assessed as being poor with a high risk of bias, mainly because of data collection and study appraisal issues (online supplemental table S3). Overlap of primary studies within the

reviews might be considered a limitation, and while no clear guidelines exist on how best to resolve it,[51] the analysis of reviews at low risk of bias indicated a high to very high overlap. In 2019, Furukawa et al found that the SSRI class and citalopram dose-response between 20 mg and 40 mg per day,[23] being at odds with reviews assessing similar datasets and those with no overlap.[61–63] On the other hand, the lack of primary studies assessing dose-response effects for older adults was a clear limitation, and warrants further investigation. Similarly the quality of primary studies is a potential limitation, but most were considered to be at low to moderate risk of bias. Furthermore, a high degree of heterogeneity existed between the 42 reviews owing to methodological diversity and the progressive development of systematic review methodologies since 1988. Despite this, the review of reviews found a general consensus between older and newer reviews that SSRIs demonstrated flat dose-response effects for the treatment of depression, and larger doses were associated with more adverse drug effects, even when reviews assessed as having a higher risk of bias were excluded. Owing to similar results being observed across and within the reviews, including data from primary and secondary care settings, the findings appear to be generalisable to routine primary and secondary care practice, and are considered as being relatively robust.

Comparison with other studies

As already acknowledged, to our knowledge, this is the first review of reviews to investigate SSRI dose-response effects. However, the findings are congruent with previous studies indicating that serotonin reuptake receptors are highly saturated when standard SSRI doses are given; exerting a ceiling effect for efficacy at standard daily doses (20 mg citalopram, fluoxetine, paroxetine; 50 mg sertraline; and 10 mg escitalopram), providing optimal receptor occupancy and serotonin effects.[10] By contrast, tricyclic antidepressants, SNRI antidepressants, and other non-SSRI antidepressants demonstrate multiple receptor effects (serotonin, norepinephrine, dopamine) with increasing doses that influence their efficacy.[11 12]

At an individual SSRI level, reviews carried out in the early 1990s indicated that citalopram, fluoxetine, paroxetine, and sertraline showed flat dose-response effects for efficacy with standard daily doses providing optimal efficacy.[56 57 59 68 72 75] Guidelines from the British Association of Psychopharmacology and Australian and New Zealand Royal College of Psychiatry have highlighted SSRI dose limitations for the treatment of depression for several years.[24 25] The recently published guidelines from the National Institute for Health and Care Excellence (NICE) advise increasing doses as one of several treatment options, and now better acknowledge dose limitations in general. However, NICE does not distinguish between drug classes,[97] and the US and Canadian guidelines fail to highlight dose limitations.[27 28]

Meaning of the study

The findings present several challenges for practice and policy makers. Firstly, these results suggest that increasing the dose might not be more effective for the treatment of depression.[24 26–28] By contrast, higher SSRI doses might be more effective for some anxiety disorders, but not others.[98 99] Therefore, future local and national depression guidelines, and standard texts such as the British National Formulary, should clearly state the difference in dose-response between drug classes, and where possible between individual antidepressants, and clearly state the need to exercise caution with higher SSRI doses.

Secondly, prescribers might find this study's findings of use when discussing and balancing drug related benefits and harms with patients and colleagues who might believe that higher doses would be more effective than standard daily doses.[31 100] The findings could help with planning follow-up reviews for patients, because previous meta-analyses have indicated that the greatest response to SSRIs occurs within the first two weeks of treatment.[101 102] One meta-analysis identified in this review indicated that 50% of response effect was achieved by four weeks of treatment.[61] Therefore, assessing response at four weeks could help to appropriately optimise treatment more quickly; reducing the average 8-12 week delay until antidepressants are switched.[100 103]

Thirdly, higher than routine daily doses could expose patients to avoidable adverse drug effects, harms, and risks, such as a greater risk of QTc prolongation, falls, hip fracture, emotional blunting, cognitive dysfunction, and drug induced anxiety and insomnia.[104–108] Some of these adverse drug effects might be mistaken for depressive symptoms that could require more follow-up appointments, treatment with a higher SSRI dose, or the coprescription of sedating antidepressants, benzodiazepines and/or antipsychotic drugs, resulting in unnecessary polypharmacy.[109–111] Furthermore, the use of higher SSRI doses could be associated with a greater risk of withdrawal symptoms that might result in prolonged treatment.[112]

Finally, as SSRIs account for 43-76% of antidepressant prescriptions in North America, Europe, and Australasia,[1 2 4 6 7] and account for more than 65% of antidepressant defined daily doses prescribed in Scotland,[4] the use of higher daily doses and a lack of prescriber awareness regarding dose limitations could be contributing to inappropriate antidepressant use and to the current growth in prescribing.[5 7–9 100]

Future research should consider examining dose-response effects with longer term SSRI use, which has increased over the years and is associated with the prescribing of higher SSRI doses.[5 7–9 113 114] The following research questions could also be considered: do placebo controlled trials demonstrate that higher SSRI doses are more effective for people experiencing loss of efficacy (tachyphylaxis) with long term treatment[115]; do neuroprogressive changes in depression affect drug response, and vice versa[116 117]; do acute on chronic depressive episodes require higher doses; does increasing or reducing doses provide non-drug effects[118 119]; and how these factors interact to affect drug response.[120] A greater focus is also needed to assess and report the achievement of remission that could help to improve patients' long term outcomes. Qualitative studies should be considered to provide insight into patients' lived experiences and expectations regarding antidepressant doses and drug limitations; as well as being used to help contextualise findings from potential quantitative studies. Lastly, a better understanding of possible dose related SSRI effects associated with withdrawals (discontinuation symptoms) could enable prescribers to support patients to discontinue treatment, as highlighted in petitions to the UK parliaments and recommendations from Public Health England and the Scottish government.[1 121–124]

Conclusion

Standard daily SSRI doses could provide a favourable balance between efficacy, acceptability, and tolerability for the acute phase (up to 12 weeks) treatment of depression in adults. Higher daily doses were associated with higher rates of early treatment discontinuation (poorer acceptability) and a higher incidence of adverse drug effects (poorer tolerability) such as, but not limited to, nausea, sexual dysfunction, fatigue, anxiety, and insomnia. We also would encourage patients to talk to their prescriber or community pharmacist if they experience adverse effects or have any concerns about their drug treatment.

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