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Review

REVIEW

Pharmacological Augmentation in Unipolar Depression: A Guide to the Guidelines

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Abstract

Background: Pharmacological augmentation is a recommended strategy for patients with treatment-resistant depression. A range of guidelines provide advice on treatment selection, prescription, monitoring and discontinuation, but variation in the content and quality of guidelines may limit the provision of objective, evidence-based care. This is of importance given the side effect burden and poorer long-term outcomes associated with polypharmacy and treatment-resistant depression. This review provides a definitive overview of pharmacological augmentation recommendations by assessing the quality of guidelines for depression and comparing the recommendations made.
Methods: A systematic literature search identified current treatment guidelines for depression published in English. Guidelines were quality assessed using the Appraisal of Guidelines for Research and Evaluation II tool. Data relating to the prescription of pharmacological augmenters were extracted from those developed with sufficient rigor, and the included recommendations compared.
Results: Total of 1696 records were identified, 19 guidelines were assessed for quality, and 10 were included. Guidelines differed in their quality, the stage at which augmentation was recommended, the agents included, and the evidence base cited. Lithium and atypical antipsychotics were recommended by all 10, though the specific advice was not consistent. Of the 15 augmenters identified, no others were universally recommended.
Conclusions: This review provides a comprehensive overview of current pharmacological augmentation recommendations for major depression and will support clinicians in selecting appropriate treatment guidance. Although some variation can be accounted for by date of guideline publication, and limited evidence from clinical trials, there is a clear need for greater consistency across guidelines to ensure patients receive consistent evidence-based care.

Key Words: Augmentation, depression, guideline, pharmacology, systematic review

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Introduction

Patients with major depression who do not respond to initial antidepressant treatment(s) may be regarded as treatment resistant and are more likely to experience poorer long-term outcomes (Fekadu et al., 2009). However, for the 25% to 50% of patients reported to have a poor response to at least 2 different antidepressant treatments (Fava and Davidson, 1996; Rush et al., 2006), outcomes can be improved with successive and multimodal treatment (Rush et al., 2006; Wooderson et al., 2014). Pharmacological augmentation—the addition of a second agent to a continued antidepressant—is one such approach, and several recent meta-analyses support the efficacy of a number of augmentation agents (Zhou et al., 2015; Strawbridge et al., 2019).

When treating patients with treatment-resistant depression (TRD), clinicians may refer to a range of guidelines published independently by local, national, and international bodies for advice on treatment selection, monitoring, and discontinuation. Such guidelines are not standardized, and a universal or "first-line" option does not exist. Therefore, treatment recommendations may vary, as may the evidence on which they are based and the overall guideline quality.

Given this potential for variation between guidelines, the poor outcomes associated with TRD, and the number of pharmacological augmentation options available, an overview of relevant guideline recommendations could prove highly valuable to both clinicians and researchers. This would help to ensure that patients receive the most appropriate, evidence-based treatment(s) and guide future research by highlighting areas of need. A recent review of treatment guidelines for depression included pharmacotherapy and neuro-stimulation but very little information pertaining to pharmacological augmentation (Bayes and Parker, 2018). The present review will therefore examine and compare guidelines for the prescription of pharmacological augmentation treatments in patients with unipolar resistant depression to provide a comprehensive overview of the recommendations made, identify consistencies and inconsistencies between them, and assess their quality. Recommendations for the development of future treatment guidelines are also made.

Methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines (Moher et al., 2009), and the study protocol was registered with PROSPERO a priori (reference: CRD42018112343).

Search Strategy and Selection Criteria

Literature searches were conducted in Embase, MEDLINE, and PsycINFO to identify guidelines published between 2008 and August 23, 2019. Titles, abstracts, and key words were searched using terms relating to guidelines, treatment, and depression as per the study protocol. All articles were evaluated for suitability by 2 independent reviewers (L.M., R.W.T.), and any discrepancies were discussed until a consensus was reached. A third review author (A.J.C.) was consulted as necessary. In addition, reference lists of identified guidelines or relevant reviews were also manually searched, and guideline websites were checked where necessary to ensure the inclusion of current guideline versions. Records identified by the search were assessed for eligibility in 2 stages.

Stage 1: Selection

All current versions of guidelines meeting the following criteria were included at this stage:

- Treatment guidelines for clinicians, meeting the following definition: statements that include recommendations intended to optimize patient care that are informed by a review of evidence and an assessment of the benefits and harms of alternative care options. This definition was adapted from Verdolini et al. (2018) and based on one created by the Institute of Medicine (Institute of Medicine [U.S.]; Graham, 2011);
- Guidelines for the management of adults (18+ years) with unipolar major depressive disorder (MDD). Recommendations for specific subsets of patients, for example, pregnant or breastfeeding women, were not included;
- Pharmacological augmentation treatment options discussed, defined as the addition of a second pharmacological agent to a continuation antidepressant. Consideration of combination therapies and augmentation with a second antidepressant medication was deemed beyond the scope of this review; and
- Published since 2008 and fully available in English.

Stage 2: Guideline Selection

All guidelines meeting stage 1 eligibility were quality assessed using the Appraisal of Guidelines for Research and Evaluation (AGREE) II tool (Brouwers et al., 2010), conducted independently by 2 of 6 review authors (R.W.T., L.M., E.O., V.A., B.V., and S.M.). All raters first completed the AGREE II online tutorial video (http://www.agreetrust.org), and all appraisals were made in line with the user manual. All items were scored from 1 (strongly disagree) to 7 (strongly agree). Scaled scores were calculated for each of the 6 domains according to the instruction manual (Hoffmann-Eßer et al., 2018). Guidelines with 3 or more domains scoring $\mu \geq 60\%$ were included, as this cut-off has been used by previous appraisals to indicate that a guideline is of reasonable quality (Brosseau et al., 2014).

Data Analysis

For guidelines reaching stage 2 inclusion, data relating to pharmacological augmentation were extracted and narratively synthesized according to the study outcomes. This included recommendations for indication/contraindication, pre-prescribing and monitoring tests, dosage, and withdrawal. Data were extracted for all pharmacological augmentation treatments recommended as first or second line (or equivalent) by at least 1 of the included guidelines. Data extraction was conducted by L.M. and R.W.T. and any discrepancies resolved through consensus.

Outcomes

Primary Outcomes

Our primary outcome is the augmentation treatments recommended by the included guidelines, including indication/contraindication, pre-prescribing and monitoring tests, dosage, and tapering/withdrawal recommendations.

Secondary Outcomes

Our secondary outcomes are discrepancies between guideline recommendations and the quality of the guidelines as assessed by the AGREE II tool.

Results

Search Results and Quality Assessment

Embase returned 1176, MEDLINE 646, and PsycINFO 513 results. The process of guideline selection can be seen in Figure 1.

Ten guidelines met the quality cut-off for inclusion (at least 3 domains with a scaled score of ≥60%). Details of included guidelines can be found in Table 1 and the scaled domain scores in Table 2. Domain scores for the 9 guidelines excluded at this stage can be found in supplementary Table 1.

General Treatment Guidance

When to Augment? Indications and Contraindications

Table 3 shows the treatment stage at which augmentation was recommended. Six guidelines recommended augmentation following 1 failed antidepressant treatment, and 4 recommended it after 2 antidepressant treatments. Varying criteria and terminology were also used to define response to prior treatments (Table 3).

Who Should Prescribe Augmentation Treatment?

The National Institute for Health and Care Excellence (NICE) guidelines stated that combinations of medications initiated in primary care should be done in consultation with a psychiatrist, and referral to specialist services/an individual with specialist interest may be appropriate. The Royal Australian and New Zealand College of Psychiatrists (RANZCP), Clinical Practice Guidelines in the Spanish NHS (CPG-S), and the World Federation of Societies of Biological Psychiatry (WFSBP) offered similar advice.

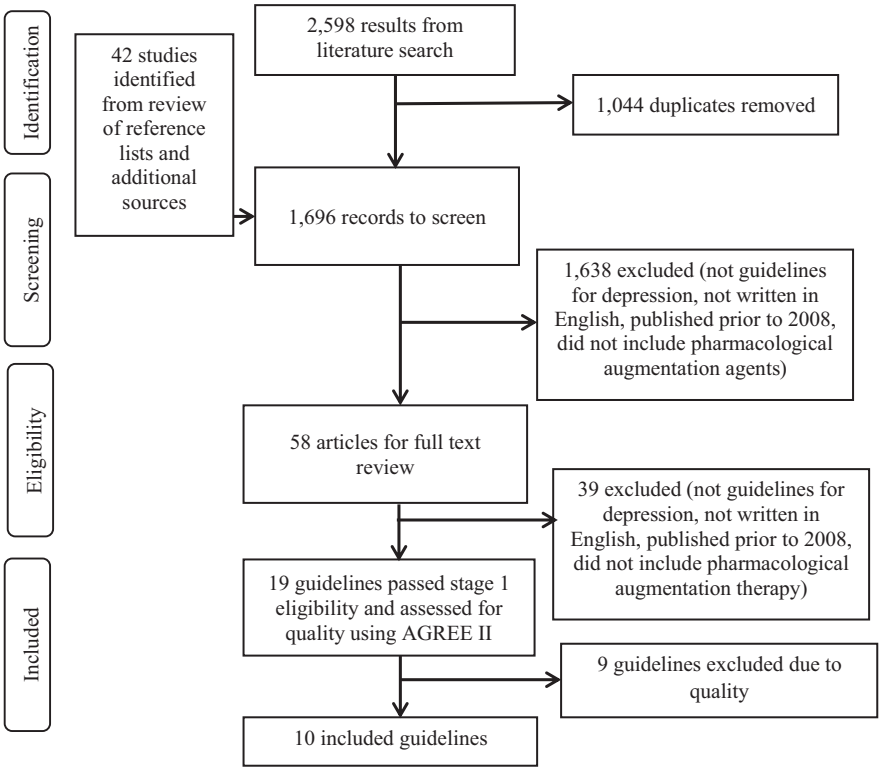

Figure 1. Guideline selection

Table 1. Included Guidelines for Augmentation Treatments in Unipolar Depression

Guideline	Region	Year
APA (American Psychiatric Association, 2010)	North America	2010
BAP (Cleare et al., 2015)	Europe	2015
CANMAT (Kennedy et al., 2016)	North America	2016
CPG-S (Ministry of Health, Social Services and Equality, Galician Agency for Health et al., 2014)	Europe	2014
ICSI (Trangle et al., 2016)	North America	2016
MPG (Taylor, David M. et al., 2018)	Europe	2018
NICE (NICE, 2009)	Europe	2009
RANZCP (Malhi et al., 2015)	Australasia	2015
TMAP (Suehs et al., 2008)	North America	2008
WFSBP (Bauer et al., 2013b, 2015)[a]	Worldwide	2013/2015

Abbreviations: APA, American Psychiatric Association; BAP, British Association of Psychopharmacology; CANMAT, Canadian Network for Mood and Anxiety Disorders; CPG-S, Clinical Practice Guidelines in the Spanish National Health Service; ICSI, Institute for Clinical Systems Improvement; MPG, Maudsley Prescribing Guidelines in Psychiatry; NICE, National Institute for Health and Clinical Excellence; RANZCP, Royal Australian and New Zealand College of Psychiatrists; TMAP, Texas Medication Algorithm Project; WFSBP, World Federation of Societies of Biological Psychiatry.

[a]Guideline parts I and II are considered together in this review

Table 2. AGREE II Scaled Domain Scores For Included Guidelines

Guideline	Domain score (%)						Mean (SD)
	Scope and purpose	Stakeholder involvement	Rigor of development	Clarity of presentation	Applicability	Editorial independence	
APA	89.9	62.5	70.0	77.8	43.8	75.0	69.7 (14.1)
BAP	80.6	61.1	47.0	75.0	50.0	79.2	65.4 (13.7)
CANMAT	80.6	62.5	53.0	94.4	27.1	66.7	64.1 (21.2)
CPG-S	100.0	93.1	83.0	80.6	85.4	83.3	87.6 (6.8)
ICSI	94.4	80.6	72.0	83.3	83.3	83.3	82.8 (6.7)
MPG	80.6	40.3	45.0	88.9	68.8	25.0	58.1 (22.9)
NICE	100.0	93.1	78.0	91.7	91.7	75.0	88.3 (8.7)
RANZCP	94.4	81.9	63.0	86.1	54.2	62.5	73.8 (14.5)
TMAP	72.2	31.9	27.0	88.9	60.4	41.7	53.6 (22.3)
WFSBP	86.1	63.9	70.0	80.6	39.6	70.8	68.5 (14.8)
Mean (SD)	87.8 (8.9)	67.1 (19.5)	60.8 (16.7)	84.7 (6.0)	60.4 (20.4)	66.3 (18.0)	

Abbreviations: APA, American Psychiatric Association; BAP, British Association of Psychopharmacology; CANMAT, Canadian Network for Mood and Anxiety Disorders; CPG-S, Clinical Practice Guidelines in the Spanish NHS; ICSI, Institute for Clinical Systems Improvement; MPG, Maudsley Prescribing Guidelines; NICE, National Institute for Health and Care Excellence; RANZCP, Royal Australian and New Zealand College of Psychiatrists; TMAP, Texas Medication Algorithm Project; WFSBP, World Federation of Societies of Biological Psychiatry.

The British Association for Psychopharmacology (BAP) and the Maudsley Prescribing Guidelines (MPG) recommended the initiation of certain augmenters in specialist centers with careful monitoring. The BAP included stimulants, estrogen in perimenopausal women, and testosterone in men with low levels, while the MPG specified lithium, ketamine, and triiodothyronine (T3). The Canadian Network for Mood and Anxiety Disorders (CANMAT) stated that their guidance was intended for psychiatrists and other mental health professionals. The Institute for Clinical Systems Improvement (ICSI), American Psychiatric Association (APA), and Texas Medication Algorithm Project (TMAP) did not advise.

Augmentation Selection/Pre-Prescription

All guidelines (except the MPG) offered general guidance about treatment selection in depression, and some included general pre-prescription assessments. General pharmacological augmentation guidance is included here, and details of pre-prescription assessments for individual augmenters are included in the relevant sections below.

TMAP took an algorithmic approach to treatment selection, while APA and RANZCP advised consideration of the side effect profile, as well as personality, lifestyle, and social factors (RANZCP). BAP recommended consideration of options with the largest evidence base and, in cases of severe TRD, consideration of multiple pharmacological combinations. NICE advocated following General Medical Council advice when prescribing augmentation off-label and recommended that clinicians document the rationale. NICE and RANZCP advised that most decisions are based on both clinical judgement and patient preference. The ICSI recommended consideration of brain imaging and pharmacogenetic testing prior to prescription in refractory disorders.

Monitoring

None of the guidelines offered general monitoring advice for augmentation beyond that relevant to all psychotropic medications (see guidelines). RANZCP was the only guideline to mention assessing for early response despite an absence of early response being the best supported predictor of augmentation treatment outcome in TRD (Taylor et al., 2019). All augmentation-specific monitoring is included in the relevant sections below.

Discontinuation

In cases of response, NICE advocated continuing both medications and, if necessary, the augmenter should be stopped before the antidepressant. For those with a higher risk of relapse, NICE recommended continuation for up to 2 years. No other general discontinuation advice was provided.

Pharmacological Augmentation Recommendations

Table 4 summarizes the augmentation agents recommended as first or second line (or equivalent) by at least 1 of the 10 included guidelines. However, guidelines varied in their categorization criteria: CANMAT's first-, second-, or third-line options were based on the level of evidence available and graded according to specific criteria; BAP, TMAP, the MPG, RANZCP, and WFSPB used similar systems, though their grading criteria were less explicit or not explained (TMAP); RANZCP distinguished between evidence-based recommendations (where there was sufficiently consistent evidence) and consensus-based recommendations (based on the collective knowledge and experience of the committee). The ICSI used the Grading of Recommendations Assessment, Development and Evaluation methodology (http://www.gradeworkinggroup.org/) and CPG-S used the Scottish

Table 3. Summary Of Defined Treatment Failures Prior To Recommendation Of Augmentation

Guideline	No. failed AD trials	Length per AD trial (weeks)	AD dose	AD response	Additional indicators for augmentation
APA	2	4–8	Sufficient	Minimal/no improvement	Consider in patients with significant side effects, i.e., if AD dose increase would not be tolerable
BAP	≥1	4	Adequate	Insufficient/partial	Good AD tolerability, AD switching unsuccessful
CANMAT	≥2	2–4	–	Partial (25–49%) or no response (<25%) reduction in severity score or nonremission at >6–8 weeks	Current AD well tolerated, patient preference for augmentation, specific residual symptoms, or side effects to be targeted
CPG-S	≥1	3–4	–	Partial/nonresponse	When deciding best treatment option, consider prior treatment resistance, risk factors, symptom profile, and severity
ICSI	≥2	6–12	–	Partial/treatment resistant	Consider augmentation after other stepped care options
MPG	2 + consideration of 3rd choice AD options[a]	3–4	–	Failed/no effect	–
NICE	Initial treatment	–	–	Nonresponse	Patient willing to tolerate increased side effect burden
RANZCP	≥1	3	Adequate	Failed	Severe/debilitating symptoms of depression
TMAP	≥1	≥4 (augmentation recommended at 6)	–	Partial (QIDS-CR 6–8) to ≥1 AD/nonresponse (QIDS-CR ≥9), or intolerance to 2 ADs[b]	–
WFSBP	≥1	2–4	Adequate	Failure/partial	–

Abbreviations: –, not stated; AD, antidepressant; QIDS-CR, Quick Inventory of Depressive Symptomatology – Clinician Rated;(Rush et al., 1996) APA, American Psychiatric Association; BAP, British Association of Psychopharmacology; CANMAT, Canadian Network for Mood and Anxiety Disorders; CPG-S, Clinical Practice Guidelines in the Spanish NHS; ICSI, Institute for Clinical Systems Improvement; MPG, Maudsley Prescribing Guidelines; NICE, National Institute for Health and Care Excellence; RANZCP, Royal Australian and New Zealand College of Psychiatrists; TMAP, Texas Medication Algorithm Project; WFSBP, World Federation of Societies of Biological Psychiatry.

[a]These included mirtazapine, vortioxetine, and agomelatine.

[b]Antidepressants must be different classes/mechanism of action.

Intercollegiate Guidelines Network system to assess evidence (Scottish Intercollegiate Guidelines Network, 2012). NICE used both Scottish Intercollegiate Guidelines Network and Grading of Recommendations Assessment, Development and Evaluation as well as considering factors such as evidence from depression in the general population, economic factors, and the values of the Guideline Development Group.

APA employed 3 levels of confidence (substantial, moderate, or may be recommended on the basis of individual circumstances), which were not clearly linked to an assessment of the evidence. Recommendations were not ranked as first or second line (or equivalents). As none of the pharmacological augmenters were recommended with "substantial confidence," they were considered either second line or "other" as appropriate in this review. As TMAP is a medication algorithm, step-by-step recommendations were divided into stages, employed according to patient response. It is not clear how closely these recommendations aligned to the evidence used, as TMAP stated "the treatment algorithms are evidence-based to the extent that evidence is available to guide treatment decisions" (Suehs et al., 2008).

Atypical Antipsychotics

AAPs: General Recommendations

First line

BAP advised that the most appropriate atypical antipsychotic (AAP) may be decided on an individual basis. An alternative may prove effective if one has failed (based on clinical experience). BAP highlighted the paucity of long-term studies and lack of research in severely treatment-resistant populations. They cited a meta-analysis in which AAPs showed benefit over placebo, though adverse effects were fourfold higher (Nelson and Papakostas, 2009). BAP also discussed a more recent meta-analysis in which response and remission rates were higher for quetiapine, aripiprazole, and risperidone, while response to olanzapine-fluoxetine combination (OFC) did not significantly differ from placebo (Spielmans et al., 2013).

AAPs were first-line equivalents in NICE, specifically aripiprazole, olanzapine, quetiapine, and risperidone, though it was not clear that this list is exhaustive. NICE concluded that the evidence for clinical efficacy was "moderate" and cautioned that dropout and side-effect reports were more likely than for antidepressant monotherapy, particularly for quetiapine (Shelton et al., 2001; Corya et al., 2006; Berman et al., 2007; Mahmoud et al., 2007; McIntyre et al., 2007; Song et al., 2007; Thase et al., 2007a; Marcus et al., 2008; Keitner et al., 2009). The absence of head-to-head trials was highlighted, and NICE suggested that similar results between treatments may be due to the low number of studies. At the time of publication, AAPs did not have UK marketing authorization for use in depression. AAP augmentation was also first line in the CPG-S, who highlighted the randomized controlled trials (RCTs) included by NICE plus an additional 8. RANZCP recommended "some" AAPs as level I augmenters and referenced placebo-controlled evidence for aripiprazole, olanzapine, quetiapine, and risperidone efficacy (Papakostas et al., 2007; Philip et al., 2008). CANMAT stated that AAPs have the most consistent evidence base of all augmentation options, though there is not enough evidence comparing with alternative adjuncts.

Second line

APA considered AAPs to be second-line augmenters and did not make agent-specific recommendations. They stated that most

trials report rapid improvements in mood, but the difference is modest compared with placebo (Shelton et al., 2001; Corya et al., 2006; Berman et al., 2007; Dorée et al., 2007; Mahmoud et al., 2007; McIntyre et al., 2007; Thase et al., 2007a; Garakani et al., 2008; Keitner et al., 2009). They also referred to trials in which OFC therapy was not significantly more effective than continued monotherapy with nortriptyline (Shelton et al., 2005) or venlafaxine (Corya et al., 2006). APA referenced the same meta-analysis as BAP (Nelson and Papakostas, 2009) in which AAP augmentation was significantly more effective than placebo. APA stressed that long-term studies were lacking at the time of publication.

TMAP recommended AAP augmentation at stage 3 of their 8-stage algorithm, making it a second-line option. TMAP included a flow chart, text descriptions, and summary medication charts in the appendix. AAPs were not included in the algorithm flow chart at stage 3 but were in the full text description. TMAP stated that there is strong evidence for the efficacy of olanzapine, aripiprazole (both Level A), and risperidone (Level B), though they are associated with adverse effects. Other AAPs, including quetiapine, were included in the appendix.

Other general recommendations

As mentioned, the ICSI did not explicitly rank their recommendations. They highlighted that AAPs were second line in the APA guidelines, and aripiprazole, quetiapine, and OFC were approved in the United States at the time of publication. The ICSI referred to a review of 3 placebo-controlled RCTs of quetiapine extended release (XR), reporting it to be effective for response and remission (Maneeton et al., 2012), and stressed that efficacy and safety should be assessed frequently (Wright et al., 2013). They also referred to 2 meta-analyses in which response and remission rates were significantly better for AAP augmentation than placebo (Papakostas et al., 2007; Nelson and Papakostas, 2009).

TMAP also included AAP augmentation of an selective serotonin reuptake inhibitor (SSRI) as an option at stage 4 if a tricyclic antidepressant (TCA) (with or without lithium or a monoamine oxidase inhibitor [MAOI]) was used at stage 3. OFC treatment was mentioned at this stage. AAPs were also included at stage 6, though the authors stated that little evidence supported recommendations at this stage, which were based on expert opinion and the consensus of the TMAP panel. Here, AAPs were recommended as part of a triple therapy approach, alongside an SSRI and bupropion.

Aripiprazole

First-Line Recommendations

BAP considered aripiprazole to be a first-line augmenter, referring to Berman et al. (2007), which demonstrated good tolerability and a higher response rate than placebo when added to a continuation antidepressant. CANMAT recommended aripiprazole supported by Level I evidence and discussed the network meta-analysis by Zhou and colleagues, which included 48 studies (n = 6645) examining the comparative efficacy of adjunctive strategies (Zhou et al., 2015). Aripiprazole and quetiapine were the only AAPs significantly more effective than placebo and were more efficacious than other options (lithium and T3). CANMAT referred to 4 additional meta-analyses (again including Nelson and Papakostas, 2009), each including 12–17 trials and reporting better efficacy for aripiprazole, quetiapine, olanzapine, and risperidone compared with placebo, with small to medium effect sizes (Komossa et al., 2010; Spielmans et al., 2013; Wen et al., 2014).

The CPG-S also specified aripiprazole as first line. They referenced 2 RCTs included by NICE (Berman et al., 2007; Marcus et al., 2008) in which the augmentation group had nonsignificantly better response and remission rates and no difference in discontinuation due to adverse effects compared with placebo. The CPG-S also referenced an RCT demonstrating the efficacy of low-dose aripiprazole in patients with an inadequate response to up to 3 antidepressants. Again, the difference in response and remission was not significant (Fava et al., 2012). An RCT of aripiprazole augmentation of clomipramine was also discussed, in which Hamilton Depression Rating Scale (HDRS) scores significantly decreased each week (Fabrazzo et al., 2012).

The WFSBP guidelines included aripiprazole as first line, citing a Cochrane study that reported aripiprazole to be significantly more effective than antidepressant monotherapy but associated with more side effects (Komossa et al., 2010). They also referenced the same double-blind RCT of low-dose aripiprazole augmentation as the CPG-S, which reported a nonsignificant effect but good tolerability (Fava et al., 2012). The MPG included aripiprazole as first line, advocating a good evidence base, good tolerability and safety, and the potential efficacy of low doses, though side effects may be disadvantageous (Papakostas et al., 2005; Simon and Nemeroff, 2005; Berman et al., 2007; Hellerstein et al., 2008; Marcus et al., 2008; Fava et al., 2012; Yoshimura et al., 2012; Jon et al., 2013).

Table 4. Summary of Pharmacological Augmentation Recommendations by Guideline

	APA	BAP	CANMAT	CPGS	ICSI	NICE	MPG	RANZCP	TMAP	WFSBP
AAPs[1]	2nd	1st	1st	1st	✔	1st	1st	1st	2nd	1st
Lithium	2nd	1st	2nd	1st	✔	✔	1st	1st	✔	1st
Other mood stabilisers	✔	2nd 1	✘	✘	–	✘	2nd 1	–	✔[a]	–
Thyroid hormones	2nd	2nd	2nd	✘	✔	✘	2nd	1st	1st	2nd
Stimulants	✔	✔	2nd[b]	–	✔	✘	✔	✘	–	–
Bupropion	✔	✔	2nd	✘	✔	✘	1st	✘	1st	✘
Buspirone	✔	✔	✘	✘	✔	✘	2nd	✘	1st	✘
Ketamine	–	✘	✔	–	✔	–	2nd	✘	–	✘

Abbreviations: 1st, first-line recommendation or equivalent; 2nd, second-line recommendation or equivalent; ✔, other recommendation/level not specified, ✘, not recommended, –, treatment not discussed by guideline; AAPs, atypical antipsychotics; APA, American Psychiatric Association; BAP, British Association of Psychopharmacology; CANMAT, Canadian Network for Mood and Anxiety Disorders; CPG-S, Clinical Practice Guidelines in the Spanish NHS; ICSI, Institute for Clinical Systems Improvement; NICE, National Institute for Health and Care Excellence; RANZCP, Royal Australian and New Zealand College of Psychiatrists; MPG, Maudsley Prescribing Guidelines; TMAP; Texas Medication Algorithm Project; WFSBP, World Federation of Societies of Biological Psychiatry.

[a]Specific combination/medication subtype recommendation.

[b]At least 1 of this class of drug recommended at indicated level.

No guidelines specifically listed aripiprazole as second line/other/not recommended.

Quetiapine

First-Line Recommendations

BAP recommended quetiapine as first line, citing evidence indicating equal efficacy to lithium (Bauer et al., 2013a) and noting that it was the only AAP licensed for use as an augmenter in the United Kingdom at the time of publication. BAP also referred to El-Khalili et al. (2010) in which quetiapine XR was significantly more effective than augmentation with placebo. CANMAT similarly recommended quetiapine as a first-line option, supported by Level I evidence.

The CPG-S referred to a comparison of quetiapine augmentation of an SSRI and venlafaxine also included by NICE in which response, remission, and depression severity did not significantly differ between groups (quetiapine did slightly better, albeit with a higher discontinuation rate; McIntyre et al., 2007). The CPG-S also mentioned Bauer et al. (2010), in which patients received quetiapine XR augmentation (150 or 300 mg) or placebo. Both groups had significantly higher remission rates compared with placebo, but only the 150-mg/d group did better in terms of response at 6 weeks. Another RCT in patients with comorbid anxiety and residual depressive symptoms demonstrated higher completion rates for quetiapine, and nonsignificantly higher response and remission rates compared with placebo were referenced as was an open-label comparison with lithium in patients unresponsive to at least 4 weeks of antidepressant treatment. HDRS scores were significantly reduced in both groups, but more so for quetiapine (Dorée et al., 2007; McIntyre et al., 2007).

The WFSBP included quetiapine as a first-line option, referencing a study in which it was significantly more effective than antidepressant monotherapy, though it has been associated with more weight gain and sedation (Komossa et al., 2010; Bauer et al. 2010), in line with CPG-S. The MPG included quetiapine as a first-line, well-tolerated augmenter with a good evidence base, advising that it should be used in addition to an SSRI or serotonin-norepinephrine reuptake inhibitors. They advised that quetiapine is possibly more effective than lithium (Montgomery et al., 2010).

No guidelines specifically included quetiapine as second line/other/not recommended.

Risperidone

First-line recommendations

The BAP recommended risperidone as first line, as did CANMAT (Level I evidence), and the CPG-S, who referred to 3 studies included in the current NICE guidelines in which there was no significant difference in depression severity or discontinuation due to adverse effects between risperidone and control (Mahmoud et al., 2007; Song et al., 2007; Keitner et al., 2009). Another study was discussed in which patients with 2 or more antidepressant failures were randomized to receive 1 of 5 augmenters, including risperidone, added to paroxetine (Fang et al., 2011). The risperidone response rate was 46.7% and remission 26.7%, with no significant difference between treatments (valproic acid buspirone, trazodone, or T3). However, the CPG-S recognized the lack of placebo arm, modest sample sizes, fixed doses, and exclusively Chinese sample as limitations.

Second-line recommendations

The MPG recommended risperidone as a second-line augmenter and cautioned that it has a small evidence base and less RCT support than other AAPs, though it is usually well tolerated. Several side effects were highlighted as disadvantages (Ostroff and Nelson, 1999; Stoll and Haura, 2000; Rapaport et al., 2006; Mahmoud et al., 2007; Yoshimura et al., 2008; Keitner et al., 2009).

Other recommendations

ICSI did not state whether they recommended the use of risperidone, but it was the only AAP highlighted as being efficacious despite not having US approval.

Not recommended

Though the WFSBP stated that risperidone was significantly more effective than antidepressant monotherapy, it was not recommended as benefits have not been sustained and it is associated with greater weight gain and prolactin change (Rapaport et al., 2006; Mahmoud et al., 2007; Reeves et al., 2008; Keitner et al., 2009).

Olanzapine

First-line recommendations

The CPG-S included olanzapine as a first-line option, referring to 2 RCTs examining OFC, also included by NICE, in which the olanzapine group had nonsignificantly better response and remission rates vs placebo (Shelton et al., 2005; Thase et al., 2007a). CPG-S also mentioned a review of 5 OFC trials that reported a significantly greater improvement in MADRS scores compared with either monotherapy with the same adverse effect levels (Trivedi et al., 2009).

The MPG recommended OFC as a first-line option, stating that it is well researched and generally well tolerated, and suggested that olanzapine augmentation of a TCA may also be effective, as may olanzapine monotherapy (Takahashi et al., 2008). The MPG highlighted the risk of weight gain and limited clinical experience outside the United States and the fact that most available data are related to bipolar disorder (Luan et al., 2017).

Second-line recommendations

The BAP recommended olanzapine as second line and concluded that olanzapine augmentation of an SSRI may be most effective when patients have been nonresponsive to SSRIs, rather than serotonin-norepinephrine reuptake inhibitors or TCAs. They referred to 2 large OFC studies in which it was more effective than fluoxetine monotherapy, but not nortriptyline continuation (Shelton et al., 2005) or venlafaxine (Corya et al., 2006), and an additional study that combined data from 1 positive and 1 negative OFC trial, which demonstrated that OFC was more effective than monotherapy (Thase et al., 2007a).

CANMAT also recommended olanzapine as a second-line augmenter, supported by Level I evidence, as did the WFSBP, concluding that the evidence was more ambiguous than for aripiprazole or quetiapine, and olanzapine was associated with more side effects, including weight gain and increase in prolactin (Komossa et al., 2010).

Brexpiprazole

Second-Line Recommendations

CANMAT recommended brexpiprazole as a second-line augmenter, supported by Level I evidence from placebo controlled trials (Thase et al., 2015a, 2015b), but highlighted that all AAPs were worse tolerated than placebo.

General AAP Dosage Recommendations

The APA, BAP, RANZCP, and the WFSBP guidelines advised that lower doses of AAPs are generally used for augmentation in TRD compared with psychosis. RANZCP cited 3 studies (Berman et al., 2007; Marcus et al., 2008; Philip et al., 2008) and highlighted that use for augmentation in unipolar TRD was off-label in Australasia at the time of publication. The ICSI recommended that dosing should be individualized, and the MPG advised that there is considerable individual variation in plasma levels, meaning monitoring is required to reach the median optimal range, if known.

CANMAT, CPG-S, NICE, and TMAP did not include general dosage guidance, but specific recommendations can be found in Tables 7–11. NICE did not make any dosage recommendations for AAPs.

General AAP Monitoring and Adverse Effect Recommendations

General side effect and/or monitoring/drug interaction guidance for AAPs was provided by APA, TMAP, the MPG, RANZCP, BAP, and CANMAT (Tables 5 and 6). The MPG stated that at least 1 abnormal liver function test is common and rarely results in significant liver damage (Marwick et al., 2012), and the majority of side effects are dose dependent. The MPG offered extensive guidance on the interaction between AAPs and street drugs, and risks of toxicity in overdose. They advised that carbamazepine may reduce the levels of most antipsychotics (Crawford, 2002; Patsalos et al., 2002; Spina and Perucca, 2002; Citrome et al., 2007).

APA warned that the side effect risk is greater than for other adjunctive strategies and tolerability can be an issue (Nelson and Papakostas, 2009). RANZCP recommended close monitoring of side effects and stressed that these are of great concern, particularly for long-term therapy.

APA warned that AAPs can inhibit metabolism via CYP2D6, which results in decreased clearance of TCAs. CANMAT similarly cautioned against concomitant administration of cytochrome P450 inhibitors (Spina et al., 2012; Brandl et al., 2014). The CGP-S stated that there may be pharmacodynamic interactions between antipsychotics and TCAs. The MPG stressed that patients should be encouraged to have good physical mobility and stay well hydrated. General monitoring recommendations are included in Table 6. See individual guidelines for more detail and frequencies. The WFSBP, ICSI, NICE, and the CPG-S gave no general side effect or monitoring guidance for AAPs. Specific guidance can be seen in Tables 7–11.

General AAP Discontinuation Recommendations

The APA stated that it is not known for how long AAP treatment should be continued when effective. RANZCP advised that gradual withdrawal should be considered once a stable response is achieved, though in some cases ongoing use is required. NICE simply stated that the risk of experiencing withdrawal/discontinuation symptoms is higher in those taking other centrally acting medications (which includes antipsychotics).

The WFSBP cited 1 study in which quetiapine in maintenance was superior to placebo in preventing relapse or recurrence of MDD (Liebowitz et al., 2010) but advised that the negative effects on metabolic function, weight gain, and tardive dyskinesia (TD) should be considered (Gao et al., 2011), and other AAPs with positive results as acute adjunctive agents have not been evaluated as maintenance treatments.

The MPG stated that AAPs should never be stopped suddenly in relation to schizophrenia and psychosis but did not clearly make the same recommendation for TRD. They recommended discontinuation if the patient's neutrophil count is

Table 5. General Side Effects for AAPs

Side effect	Guideline(s)
Weight gain	APA (Andersen et al., 2005), TMAP, RANZCP
Other metabolic complications/metabolic syndrome	RANZCP
Glucose dysregulation/diabetes mellitus	APA
Dyslipidaemia	Hypertriglyceridemia (APA), hypercholesterolemia and hyperglycemia (particularly for olanzapine; TMAP)
Hyperprolactinemia	APA, MPG
QTc prolongation	APA, BAP (Haddad and Anderson, 2002; Leucht et al., 2013), MPG
Coronary heart disease/risk of sudden cardiac death	MPG (Ray et al., 2001; Hennessy et al., 2002; Reilly et al., 2002; Straus et al., 2004; Liperoti et al., 2005; Osborn et al., 2007; Stroup et al., 2009; Murray-Thomas et al., 2013)
Extrapyramidal side effects (including tardive dyskinesia and neuroleptic malignant syndrome)[a]	NICE, MPG (Baldessarini et al., 1988; Peluso et al., 2012), RANZCP, APA, TMAP
Acute kidney injury	MPG
Sedation	MPG
Postural hypotension	MPG
Anticholinergic effects	MPG
Hyponatraemia	MPG (Littrell et al., 1997; Kawai et al., 2002; Montgomery and Tekell, 2003; Meulendijks et al., 2010)
Sexual dysfunction	MPG
Increased risk of pneumonia	MPG
Increased risk of thromboembolism	MPG (Zhang et al., 2011; Barbui et al., 2014)

Abbreviations: APA, American Psychiatric Association; BAP, British Association of Psychopharmacology; CANMAT, Canadian Network for Mood and Anxiety Disorders; CPG-S, Clinical Practice Guidelines in the Spanish NHS; ICSI, Institute for Clinical Systems Improvement; NICE, National Institute for Health and Care Excellence; QTc, corrected QT interval; RANZCP, Royal Australian and New Zealand College of Psychiatrists; MPG, Maudsley Prescribing Guidelines; TMAP; Texas Medication Algorithm Project; WFSBP, World Federation of Societies of Biological Psychiatry.

[a]See individual guidelines for specific symptoms.

Table 6. General Pre-Prescription and Monitoring Tests for AAPs

Test/examination	Guidelines(s)
ECG	BAP, TMAP, MPG
Pregnancy test (as indicated)	TMAP
Extrapyramidal side effects	TMAP
Weight/BMI	NICE, TMAP, MPG
Glucose levels	NICE, TMAP, MPG
Lipid levels	NICE, TMAP, MPG
Sexual function enquiry	TMAP
Prolactin level	TMAP[a], MPG
Ocular evaluations	TMAP
Urea and electrolytes	MPG (Leucht et al., 2005; Agid et al., 2006; Zhang et al., 2013; Subotnik et al., 2015; Zhu et al., 2017; Robinson et al., 2018)
Full blood count	MPG (Leucht et al., 2005; Agid et al., 2006; Zhang et al., 2013; Subotnik et al., 2015; Zhu et al., 2017; Robinson et al., 2018)
Blood pressure	MPG
Liver function tests	MPG (Olofinjana and Taylor, 2005; Haro et al., 2006; Stroup et al., 2006)
Signs of chest infection	MPG

Abbreviations: BAP, British Association of Psychopharmacology; BMI, body mass index; ECG, electrocardiogram; NICE, National Institute for Health and Care Excellence; MPG, Maudsley Prescribing Guidelines; TMAP, Texas Medication Algorithm Project.
*a*If evidence of galactorrhoea/gynecomastia, menstrual disturbance, libido disturbance or erectile/ejaculatory disturbance in males

<1.5*10^9/L, or if liver function tests indicate hepatitis or functional damage. If blood lipids or blood pressure are out of range, switching to another antipsychotic is advised. They also recommended switching drugs in cases of confirmed and symptomatic hyperprolactinemia, and discontinuation/switching if akathisia, weight gain, increase in plasma lipids, neuroleptic malignant syndrome, hyperglycemia, hyperprolactinemia, or sexual dysfunction are experienced. They advised that AAPs are probably safe to restart at the previous dose following a period of noncompliance.

Lithium

First-line lithium recommendations

The BAP recommended lithium as a first-line augmenter but cautioned that most studies augmented TCAs and the association with side effects. BAP discussed the lack of head-to-head comparisons, again mentioning the 2013 study in which quetiapine XR was at least as effective as lithium over 6 weeks (Bauer et al., 2013a), a randomized open comparison with lamotrigine in which lithium was nonsignificantly better (Schindler and Anghelescu, 2007a), and a meta-analysis of EU-licensed augmenters with similar response rates for lithium, quetiapine XR, and S-adenosyl-L-methionine, though S-adenosyl-L-methionine was significantly better compared directly with lithium (Turner et al., 2014). Finally, BAP discussed a blind-rated comparison with cognitive behavioral therapy (CBT) augmentation by Kennedy et al. (2003), which found a nonsignificant advantage of lithium at 8 weeks and 4 weeks post discontinuation.

The BAP highlighted the reduced risk of suicide associated with lithium compared with antidepressant monotherapy, which they claimed was supported by Level I evidence (not cited). They stated that modest, but reasonably sound evidence exists for lithium augmentation of an MAOI, referring to a meta-analysis of 10 small RCTs (Crossley and Bauer, 2007). A study in which lithium augmentation was used at stage 2 of a 4-step inpatient treatment program with a 59% response rate was also referred to (Birkenhäger et al., 2006), contrasting with the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, in which just 16% of participants reached remission with lithium as a third-stage treatment. The BAP suggested this may be due to greater comorbidity rates, degree of resistance, and unknown adequacy of lithium treatment in STAR*D (Nierenberg et al., 2006). They also included a systematic review of 30 open-label and 10 placebo-controlled studies with relatively small sample sizes (Bauer et al., 2014). The BAP briefly discussed outcome prediction with lithium augmentation and highlighted the association between better outcomes and greater depressive symptomatology, significant weight loss, psychomotor retardation, a history of more than 3 depressive episodes, and a family history of major depression (not referenced).

The RANZCP guidelines also considered lithium augmentation to have Level I evidence, stating that it is widely used and supported and is more effective than placebo when used with TCAs, SSRIs, and other antidepressants (Bauer et al., 2000; Crossley and Bauer, 2007). Like BAP, RANZCP discussed predictors of lithium response, including a history of more than 3 prior depressive episodes and first-degree family history of bipolar or unipolar depression (Sugawara et al., 2010), as well as the predictive power of early response, stating that if no benefit is found within 7–10 days, alternative treatments should be considered (not referenced).

The WFSBP guidelines stated that there is evidence for use of lithium with a range of antidepressants, including TCAs (Joffe et al., 1993; Katona et al., 1995) and SSRIs (Katona et al., 1995; Baumann et al., 1996; Zullino and Baumann, 2001). A meta-analysis also mentioned by BAP was cited (Crossley and Bauer, 2007), as was the STAR*D comparison of T3 and lithium augmentation in which there was no significant difference in remission rates, but fewer side effects and dropouts for T3 (Nierenberg et al., 2006). WFSBP noted that lithium was effective in preventing suicide/suicide attempts, but it is not known if it has acute anti-suicide effects (Coppen et al., 1990; Thies-Flechtner et al., 1996; Tondo et al., 1997; Müller-Oerlinghausen, 1999; Schou, 2000; Guzzetta et al., 2007; Lauterbach et al., 2008; Cipriani et al., 2013).

The CPG-S recommended lithium as a first-line option, supported by Level B evidence, following nonresponse by the third or fourth week of antidepressant treatment, or at later stages in treatment, supported by Level C evidence. The CPG-S were predominantly reliant on the evidence and recommendations in the current NICE (2009) guidelines and stated that these data

Table 7. Aripiprazole Dosage and Monitoring Guidance

Guideline	Dose	Patient monitoring parameters	Specific side effects	Specific drug interactions
APA	2.5–5 mg/d, titrated to a max of 15 mg/d (Berman et al., 2007)	General AAP guidance only	General AAP guidance only	General AAP guidance only
BAP	2.5–10 mg/d (Taylor et al., 2015)	General AAP guidance only	General AAP guidance only	–
CANMAT	2–15 mg/d	–	–	Moderate potential for drug-drug interactions (2D6, 3A4 substrate)
CPG-S	–	–	Weight gain, dry mouth, constipation (Fava et al., 2012)	–
ICSI	General AAP guidance only	–	Higher rates of akathisia and fatigue compared with placebo (Berman et al., 2007; Marcus et al., 2008)	–
MPG	2–10 mg/d	General AAP guidance, plus caution required in cases of severe hepatic impairment. General monitoring advice applies, but lipids and blood pressure may not be required, and less monitoring of weight compared with other AAPs.	General AAP guidance, plus akathisia and restlessness common, and insomnia may be problematic. Caution required in cases of severe hepatic impairment due to findings of increased LFTs, hepatitis, and jaundice (Mallikaarjun et al., 2008; Datapharm Communications Ltd, 2017; Truven Health Analytics, 2018). Very low risk (in relation to other AAPs) for sedation, weight gain, parkinsonism, anticholinergic effects, hypotension, and prolactin level changes. Low risk of akathisia. Low relative effect on QTc. No reported AEs on sexual function. Cases of hypersexuality have been reported (Chen et al., 2011; Vrignaud et al., 2014).	General AAP guidance/ refer to guidelines
NICE	–	–	–	–
RANZCP	General AAP guidance only	General AAP guidance only	General AAP guidance only	–
TMAP	10 mg/d, titrated by 5 mg/d to 10–20 mg/d	General AAP guidance only	General AAP guidance, plus agitation, constipation, EPS, Insomnia, nausea, somnolence	Carbamazepine, fluoxetine, ketoconazole, paroxetine, quinidine, St John's wort
WFSBP	2–5 mg/d initially, adjustments of up to 5 mg/d no less than once p/w, maximum 15 mg/d	–	Weight gain, akathisia	–

Abbreviations: –, not reported by guideline; AAPs, atypical antipsychotics; AEs, adverse effects; APA, American Psychiatric Association; BAP, British Association of Psychopharmacology; CANMAT, Canadian Network for Mood and Anxiety Disorders; CPG-S, Clinical Practice Guidelines in the Spanish NHS; ICSI, Institute for Clinical Systems Improvement; EPS, extrapyramidal side-effects; LFTs, liver function tests; NICE, National Institute for Health and Care Excellence; RANZCP, Royal Australian and New Zealand College of Psychiatrists; MPG, Maudsley Prescribing Guidelines; p/w, per week; QTc, corrected Q-T interval; TMAP, Texas Medication Algorithm Project; WFSBP, World Federation of Societies of Biological Psychiatry.

Table 8. Quetiapine Dosage and Monitoring

Guideline	Dose	Patient monitoring parameters	Specific side effects	Specific drug interactions
APA	25-400 mg/d	General AAP guidance only	General AAP guidance only	General AAP guidance only
BAP	No specific recommendations but cited Vieta et al., 2013 and not El-Khalili et al., 2010 in relation to dosing (El-Khalili et al., 2010; Vieta et al., 2013)	General AAP guidance only	General AAP guidance only	–
CANMAT	150–300 mg/d	–	Cautioned in patients with prolonged QT interval	High potential for drug-drug interactions (3A4 substrate). Increases serum levels of CYP34A CYP substrates.
CPG-S	–	–	–	–
ICSI	General AAP guidance only	–	–	–
MPG	150 or 300 mg/d. See guidelines for recommendations in cases of hepatic impairment	General AAP guidance, plus annual thyroid function tests	General AAP guidance, plus dry mouth, sedation, constipation, weight gain risk in longer term. Transient rises in AST, ALT and GGT, rarely jaundice and hepatitis. Severe cases of fatal hepatic failure and hepatocellular damage reported (Preskorn, 2012; Das et al., 2017; Datapharm Communications Ltd, 2017; Truven Health Analytics, 2018). Very low relative risk of akathisia, parkinsonism, and prolactin elevation. Low relative risk of anticholinergic effects, moderate relative risk of sedation, weight gain and hypotension. Moderate relative risk of effect on QTc. Small risk of TFT abnormality (Remington et al., 2007; Leucht et al., 2009). Moderate propensity for increasing plasma lipids (Smith et al., 2010). Low risk of sexual dysfunction (Bobes et al., 2003; Byerly et al., 2004; Knegtering et al., 2004; Montejo González et al., 2005), but studies conflicting(Atmaca et al., 2005; Kelly and Conley, 2006).	General AAP guidance/see guidelines

Table 8. Continued

Guideline	Dose	Patient monitoring parameters	Specific side effects	Specific drug interactions
NICE	–	–	–	–
RANZCP	General AAP guidance only	General AAP guidance only	General AAP guidance, plus high levels of sedation	–
TMAP	100 mg/d x 3 days, then 200 mg/d, max 400 mg/d (target range 150–400 mg/d)	General AAP guidance only	General AAP guidance, plus cataract formation, dry mouth, glucose dysregulation, headache, hyperlipidaemia, increased appetite, orthostatic hypotension, sedation, weight gain	Erythromycin, fluconazole, ketoconazole, phenytoin, St John's wort, thioridazine, valproate
WFSBP	50 mg/d, increased to 150 mg at day 3, increased to 300 mg/d dependent on response. Higher doses not studied as add on for TRD	–	Sedation, weight gain	–

Abbreviations: –, not reported by guideline; AAPs, atypical antipsychotics; ALT, alanine aminotransferase; APA, American Psychiatric Association; AST, aspartate aminotransferase; BAP, British Association of Psychopharmacology; CANMAT, Canadian Network for Mood and Anxiety Disorders; CPG-S, Clinical Practice Guidelines in the Spanish NHS; GGT, gamma-glutamyl transpeptidase; ICSI, Institute for Clinical Systems Improvement; MPG, Maudsley Prescribing Guidelines; NICE, National Institute for Health and Care Excellence; QTc, corrected Q-T interval; RANZCP, Royal Australian and New Zealand College of Psychiatrists; TMAP, Texas Medication Algorithm Project; TFT, thyroid function test; TRD, treatment resistant depression; WFSBP, World Federation of Societies of Biological Psychiatry.

show significantly better response rates compared with placebo and nonsignificantly better remission rates. They also indicated that lithium was less well tolerated and highlighted the possibility of greater adverse effects when initiating lithium.

In addition to citing evidence included by NICE, the CPG-S considered 2 more recent articles: the STAR*D comparison of lithium and T3 augmentation (Nierenberg et al., 2006) and a multi-step algorithmic study, which by contrast reported that lithium augmentation had higher rates of remission than T3 (Gervasoni et al., 2009). Finally, a study that reported no difference in severity or response/remission between lithium and lamotrigine over 8 weeks was referenced (Schindler and Anghelescu, 2007a).

Other evidence considered by the CPG-S included the RCT comparison of lithium and CBT discussed by BAP (Kennedy et al., 2003), a systematic review of 11 studies in which antidepressant dose increase was no less effective than augmentation with either lithium or desipramine (Adli et al., 2005), and the 2007 comparison of lithium and quetiapine augmentation demonstrating no significant difference, also mentioned in relation to quetiapine by the CPG-S and APA (Dorée et al., 2007).

The MPG advised that lithium is well established and well supported in the literature and recommended by NICE, but there is poor tolerability at higher plasma levels, potential toxicity, and a need for plasma monitoring and specialist referral. They highlighted that it may not be effective in patients resistant to multiple treatments (Fava et al., 1994; Bauer and Dopfmer, 1999; Nierenberg et al., 2003, 2006; Crossley and Bauer, 2007). Again, STAR*D was mentioned, (Nierenberg et al., 2006) as well as the current BAP guidelines (Cleare et al., 2015), and the ongoing Lithium vs Quetiapine in Depression study which seeks to determine whether lithium or quetiapine is most effective when compared head-to-head over 12 months (Marwood et al., 2017). The MPG suggested the following characteristics may predict a better response to lithium: greater severity in depressive symptoms, psychomotor retardation, significant weight loss, family history of MDD, and personal history of at least 3 depressive episodes (Bauer et al., 2014). The MPG advised that treatment adherence should be included, and they also raised the potential protective effect against suicide, though the mechanism of this effect remains unknown (Cipriani et al., 2013).

Second-line recommendations

APA included lithium with Level II (moderate) confidence and stated that it is the most widely studied adjunctive treatment for this patient group, has the potential to reduce the risk of suicide, and has efficacy in preventing relapse (Austin et al., 1991; Bauer and Dopfmer, 1999; Cipriani et al., 2006; Crossley and Bauer, 2007). Again, the STAR*D comparison of lithium and T3 was discussed (Nierenberg et al., 2006). APA advised that the time from initiation to full response can range from a few days to 6 weeks.

CANMAT also recommended lithium as a second-line option, supported by Level II evidence. As one of the more recently published guidelines in this review, CANMAT discussed the network meta-analysis comparing the adjunctive effects of pharmacological augmenters with each other and placebo (Zhou et al., 2015). Only olanzapine, lithium, quetiapine, and T3 were more effective than placebo, and stronger efficacy was reported for the AAPs than for lithium and T3. CANMAT also referenced a 2014 systematic review that concluded that lithium was effective, though the sample sizes of the 10 included trials were small, as well as an additional meta-analysis of placebo-controlled RCTs demonstrating efficacy and the STAR*D comparison of lithium

Table 9. Risperidone Dosage and Monitoring

Guideline	Dose	Patient monitoring parameters	Specific side effects	Specific drug interactions
APA	Up to 3mg/d	General AAP guidance only	General AAP guidance, plus prolactin related side effects	General AAP guidance only
BAP	0.5-2mg/d.(Taylor et al., 2015)	General AAP guidance only	General AAP guidance only	–
CANMAT	1-3mg/d	–	–	Moderate potential for drug-drug interactions (2D6, 3A4 substrate). Increases serum levels of CYP1A2 CYP substrates and CYP2D6.
CPG-S	–	–	–	–
ICSI	General AAP guidance only	–	–	–
MPG	General AAP guidance, plus 0.5-3mg/d, see guidelines for recommendations in cases of hepatic impairment	General AAP guidance only	Transient asymptomatic elevations in LFTs, cholestatic hepatitis, jaundice and rare cases of hepatic failure reported (Atasoy et al., 2007; Preskorn, 2012; Datapharm Communications Ltd, 2017; Truven Health Analytics, 2018). Low relative risk of sedation, akathisia, parkinsonism, and anticholinergic effects. Moderate relative risk of weight gain and hypotension, and high incidence of prolactin elevation (avoid in patients under 25/ osteoporosis/history of hormone dependent breast cancer). Low relative risk of effect on QTc. Moderate propensity for increasing plasma lipids.(Perez-Iglesias et al., 2009) Moderately high reported incidence of ejaculatory problems (Dubé et al., 2007; Tohen et al., 2012). Priapism reported rarely (Baldwin and Mayers, 2003). Prevalence of sexual dysfunction reported to be 60–70% (Serretti and Chiesa, 2011).	General AAP guidance/see guidelines
NICE	–	–	–	–
RANZCP	General AAP guidance only	General AAP guidance only	General AAP guidance only	May be less effective in poor CYP2D6 metabolisers (de Leon et al., 2010).
TMAP	0.25-0.5mg/d, target range 1-2mg/d	General AAP guidance only	General AAP guidance, plus EPS, glucose dysregulation, galactorrhoea, hyperlipidaemia, menstrual irregularity, orthostatic hypotension, prolactin elevation, sedation, sexual dysfunction, tardive dyskinesia, weight gain	Carbamazepine, cimetidine, fluoxetine, paroxetine, phenytoin, rifampin, tricyclic antidepressants.
WFSBP	Not recommended			

Abbreviations: –, not reported by guideline; AAPs, atypical antipsychotics; APA, American Psychiatric Association; BAP, British Association of Psychopharmacology; CANMAT, Canadian Network for Mood and Anxiety Disorders; CPG-S, Clinical Practice Guidelines in the Spanish NHS; ICSI, Institute for Clinical Systems Improvement; LFTs, liver function tests; NICE, National Institute for Health and Care Excellence; MPG, Maudsley Prescribing Guidelines; QTc, corrected Q-T interval; RANZCP, Royal Australian and New Zealand College of Psychiatrists; TMAP, Texas Medication Algorithm Project; WFSBP, World Federation of Societies of Biological Psychiatry.

Table 10. Olanzapine Dosage and Monitoring

Guideline	Dose	Patient monitoring parameters	Specific side effects	Specific drug interactions
APA	25 mg/d fluoxetine plus 6 mg/d olanzapine, 18 mg/d max	General AAP guidance only	General AAP guidance plus long-term weight gain	General AAP guidance only
BAP	2.5–10 mg/d olanzapine	General AAP guidance only	General AAP guidance only	–
CANMAT	2.5–10 mg/d olanzapine	–	–	Moderate potential for drug-drug interactions (1Ae substrate) and is also metabolized through the uridine diphosphate glucuronosyltransferase pathway. Increases serum levels of CYP1A2 CYP substrates and CYP2D6.
CPG-S	–	–	Weight gain, dry mouth, appetite increase, fatigue, drowsiness, headache, and edema occurring in ≥10% of patients (Trivedi et al., 2009)	–
ICSI	General AAP guidance only	–	–	–
MPG	6.25–12.5 mg/d olanzapine plus 25–50 mg/d fluoxetine	Special precaution to be taken with plasma glucose, which should be checked at baseline, 1 month, and then every 4–6 months	Sedation, anticholinergic, caution advised in hepatic impairment. Reports of transient asymptomatic elevations in ALT and AST in physically healthy adults (Atasoy et al., 2007; Preskorn, 2012; Datapharm Communications Ltd, 2017; Truven Health Analytics, 2018). Very low risk (in relation to other AAPs) of akathisia and parkinsonism. Low relative risk of anticholinergic effects, hypotension, and prolactin elevation. Moderate relative risk of sedation, high relative risk of weight gain. Low relative risk of effects on QTc. Highest propensity for increasing plasma lipids (Chaggar et al., 2011). Prevalence of sexual dysfunction reported to be >50% (Serretti and Chiesa, 2011), priapism reported rarely (Dossenbach et al., 2006).	General AAP guidance/refer to guidelines
NICE	–	–	–	–
RANZCP	General AAP guidance and lower dose in elderly	General AAP guidance only	General AAP guidance, plus very sedating, increased appetite, metabolic syndrome	–
TMAP	5–10 mg/d, titrated by 5 mg/d to 10–20 mg/d	General AAP guidance only	General AAP guidance, plus constipation, dizziness, dry mouth, glucose dysregulation, hyperlipidaemia, increased appetite, sedation, weight gain	Carbamazepine, fluvoxamine, rifampicin, smoking, St John's wort
WFSBP	General AAP guidance only	–	–	–

Abbreviations: ··, not reported by guideline; AAPs, atypical antipsychotics; APA, American Psychiatric Association; BAP, British Association of Psychopharmacology; CANMAT, Canadian Network for Mood and Anxiety Disorders; CPG-S, Clinical Practice Guidelines in the Spanish NHS; ICSI, Institute for Clinical Systems Improvement; NICE, National Institute for Health and Care Excellence; MPG, Maudsley Prescribing Guidelines; RANZCP, Royal Australian and New Zealand College of Psychiatrists; TMAP, Texas Medication Algorithm Project; WFSBP, World Federation of Societies of Biological Psychiatry.

Table 11. Brexpiprazole Dosage and Monitoring

Guideline	Dose	Patient monitoring parameters	Specific side effects	Specific drug interactions
APA	Not recommended			
BAP	Not recommended			
CANMAT	1–3 mg/d	–	–	–
CPG-S	Not recommended			
ICSI	Not recommended			
MPG	Not recommended			
NICE	Not recommended			
RANZCP	Not recommended			
TMAP	Not recommended			
WFSBP	Not recommended			

Abbreviations: –, not reported by guideline; AAPs, atypical antipsychotics; APA, American Psychiatric Association; BAP, British Association of Psychopharmacology; CANMAT, Canadian Network for Mood and Anxiety Disorders; CPG-S, Clinical Practice Guidelines in the Spanish NHS; ICSI, Institute for Clinical Systems Improvement; NICE, National Institute for Health and Care Excellence; RANZCP, Royal Australian and New Zealand College of Psychiatrists; MPG, Maudsley Prescribing Guidelines; TMAP, Texas Medication Algorithm Project; WFSBP, World Federation of Societies of Biological Psychiatry.

and T3 (Nierenberg et al., 2006; Bauer et al., 2014; Nelson et al., 2014).

Other recommendations

The ICSI recommended lithium augmentation of TCAs and advised caution when augmenting SSRIs in light of serotonin syndrome reports (not referenced). Seven placebo-controlled trials demonstrating the efficacy of lithium augmentation were mentioned, though not all were referenced (Delgado et al., 1988; Joffe et al., 1993; Katona et al., 1995; Baumann et al., 1996). The STAR*D comparison with T3 was also included (Nierenberg et al., 2006). The ICSI also noted studies in which increasing the antidepressant dose proved more effective than adding lithium (Fava et al., 1994; Perry et al., 1994).

NICE included lithium augmentation but did not specify the level of recommendation. They included 10 eligible RCTs, all of which were between 1 and 6 weeks in length and had been included in their previous guidelines (Zusky et al., 1988; Jensen et al., 1992; Joffe et al., 1993; Stein and Bernadt, 1993; Baumann et al., 1996; Shahal et al., 1996; Bloch et al., 1997; Cappiello et al., 1998; Januel et al., 2002; Nierenberg et al., 2006). NICE concluded that there was some evidence that lithium augmentation was effective in reducing the symptoms of depression and stressed that although lithium appears to be less acceptable than placebo, there was not enough evidence to determine whether this is due to the side-effect burden.

TMAP recommended lithium at stages 3 and 4 of their algorithm, making it a third- or fourth-line augmenter. They specifically recommended the use of lithium in addition to a TCA, but no evidence was cited to support these recommendations.

Dosage, monitoring, and adverse effects

Dosing, monitoring, and adverse effects recommendations for lithium are summarized in Table 12.

Discontinuation

The discontinuation recommendations for lithium are summarized in Table 13.

Anticonvulsant Mood Stabilizers

Second-line recommendations

BAP recommended lamotrigine as a second-line augmenter but stated that few studies support the use of anticonvulsants, citing trials showing limited efficacy (Barbee and Jamhour, 2002; Barbosa et al., 2003) and 1 study already referred to in which lamotrigine was comparable with lithium (Schindler and Anghelescu, 2007a). The MPG also listed lamotrigine as a second-line option, suggesting that it may be the best tolerated augmentation strategy, supported by 3 trials (Normann et al., 2002; Barbosa et al., 2003; Santos et al., 2008) and 1 retrospective chart review (Barbee and Jamhour, 2002).

Other recommendations

TMAP featured lamotrigine augmentation at stage 3a as an option for partial responders to stage 3. Lamotrigine was also included at stage 6 of TMAP, but no supporting evidence was cited.

APA advised that lamotrigine and other anticonvulsants such as carbamazepine and valproic acid may be beneficial in TRD but have not been extensively evaluated for this purpose (Cullen et al., 1991; Barbosa et al., 2003; Fava et al., 2006; Trivedi et al., 2006a; Schindler and Anghelescu, 2007b). APA also cautioned that anticonvulsant compounds may negatively impact mood (Schmitz, 2002), as some, including barbiturates and potentially vigabatrin, have been associated with an increased risk of depression (Levinson and Devinsky, 1999) supported by a statement from the US Food and Drug Administration (Kuehn, 2008).

Not recommended

NICE did not recommend lamotrigine, carbamazepine, or valproate as they considered the evidence inadequate at the time of publication (Hurley, 2002; Normann et al., 2002; Barbosa et al., 2003; Schindler and Anghelescu, 2007b; Santos et al., 2008) as did CANMAT (Zhou et al., 2015). NICE acknowledged that lamotrigine is generally well tolerated and has no major drug interactions and suggested that further trials are warranted given the existing evidence in epilepsy and bipolar disorder, though there is no evidence to suggest other anticonvulsants (e.g., gabapentin and topiramate) might be useful. There was just 1 open label study assessing valproate augmentation in unipolar depression at the time of publication (Davis et al., 1996) as existing evidence has indicated it is more effective in hypomanic rather than depressed states in bipolar disorder. NICE cited limited research examining carbamazepine in unipolar depression, with several open-label studies and 1 RCT showing benefit (Cullen et al., 1991; Ta Ketter, 1997; Dietrich and Emrich, 1998; Zhang et al., 2008). They also noted that many older patients responding to carbamazepine discontinued due to adverse effects (Cullen et al., 1991).

The CPG-S referred to the evidence base included by NICE for lamotrigine plus 2 additional RCTs (Nierenberg et al., 2006;

Table 12. Lithium Monitoring and Dosing

Guideline	Dose	Patient monitoring parameters	Specific side effects	Specific drug interactions
APA	Required blood level not confirmed	–	Caution with Parkinson's as may worsen symptoms	–
BAP	Referred to a study in which plasma lithium levels of 0.6–1.2 mmol/L were more effective than those outside this range (Bauer et al., 2013a) and a meta-analysis in which most studies used 600–1200 mg/d (not clear recommendations; Crossley and Bauer, 2007)	–	–	–
CANMAT	600–1200 mg/d, dosing 1-2x p/d, aiming for "therapeutic serum levels" (not specified)	–	–	–
CPG-S	–	–	–	–
ICSI	Referred to studies with usual dose of 300 mg/d administered 3 times during the day, serum levels >0.4 mmol/L (not a clear recommendation; Joffe et al., 1993; Katona et al., 1995; Baumann et al., 1996)	–	–	–
MPG	Plasma level 0.4–0.8 mmol/L, increased to 1.0 mmol/L if response suboptimal. 0.6 mmol/L minimum level for prophylaxis/ maintenance. See guidelines for recommendations by lithium preparation and advice for impaired renal function. Lithium levels >0.8 mmol/L associated with higher risk of renal toxicity. Toxic effects occur at levels >1.5 mmol/L. Optimal plasma range less clear in unipolar than bipolar depression (Young, 2017).	Baseline: renal, thyroid, and cardiac function estimated GFR and TfTs as a minimum (Morriss and Benjamin, 2008). ECG in all patients with cardiovascular disease risk factors. Weight. Calcium levels desirable. Testing thyroid autoantibodies to aid elimination of hypothyroidism risk. Women advised to use contraception. Serum levels tested after 12 h in patients taking 1 daily dose at bedtime (Goodwin et al., 2016). For middle-aged women, TfTs monitored regularly in first year plus monitoring calcium levels (Livingstone and Rampes, 2006). Plasma lithium, eFGR, and TfTs every 6 mo in all patients and more regularly in special populations. Weight/ BMI monitoring. Calcium level monitoring desirable. Renal function monitored regularly in prolonged treatment (Aiff et al., 2015).	Mild GI upset, tremor, polyurea (Bowen et al., 1991; Ljubicic et al., 2008), thirst, polydipsia. Can cause diuresis and tolerance difficulties in patients with bladder disorder. Contraindicated in severe renal impairment (Gitlin, 1999; Lepkifker et al., 2004). Long-term use associated with impaired renal function, nephrogenic diabetes insipidus, nephrotic syndrome, and both reversible, irreversible kidney damage and increased risk of hypothyroidism (Johnston and Eagles, 1999; Frye et al., 2009; McKnight et al., 2012; Shine et al., 2015). Lithium associated with hyperparathyroidism (McKnight et al., 2012) and chronically elevated calcium levels associated with renal stones, osteoporosis, dyspepsia, hypertension, and renal impairment. May aggravate skin conditions, cause metallic taste, ankle edema, and weight gain. NMS sometimes seen (Gill et al., 2003). Impaired visual adaptation to dark (Metzner et al., 1993). Moderate caution advised in epilepsy as limited evidence of effect on seizures (Wickstrøm et al., 1980). Association with Ebsteins abnormality (though risk may be overestimated; McKnight et al., 2012; Diav-Citrin et al., 2014). Contraindicated in pregnancy. See guidelines for advice on toxicity symptoms and overdose.	Drugs altering renal sodium handling can precipitate lithium toxicity. Includes ACE inhibitors, thiazide diuretics, and NSAIDS. Rare reports of neurotoxicity with carbamazepine. Street drugs can be very toxic if taken erratically. Caffeine cautioned as may decrease lithium levels and withdrawal from caffeine may increase (Baethge et al., 2009).
NICE	Plasma levels 0.5–1.0 mmol/L considered therapeutic; toxicity may develop >1.5 mmol/L and can lead to death at 2.0 mmol/L	Baseline and at least every 6 mo: renal function, TFTs. Lithium levels at 1 wk and after every dose change until stable, then every 3 mo. ECG monitoring for patients with high risk of CVD/ cardiac symptoms. NICE referred to their bipolar guidelines for further monitoring advice.	Range of cardiac effects: may be important in heart disease, elderly, high lithium levels, hypokalaemia, or those prescribed diuretics, hydroxyzine, and TCAs (Chong et al., 2001). Potential for "sick sinus" syndrome, first-degree heart block, ventricular ectopics, flattened T-waves, and increased QT dispersion, which are common and often subclinical (Reilly et al., 2000). Can also cause hypothyroidism and renal damage, among other effects.	Can interact with commonly prescribed drugs precipitating toxicity. See guidelines for advice on interactions with drugs used during surgery.

Table 12. Continued

Guideline	Dose	Patient monitoring parameters	Specific side effects	Specific drug interactions
RANZCP	Trough plasma level (12 h after dosing) between 0.5 and 0.8mmol/L (Berghöfer et al., 2006; Malhi et al., 2011)	Baseline: FBC, renal function, thyroid function, and calcium levels. Check for pregnancy using hCG. At 6, 12, and 24 mo: renal function (urea, creatinine, electrolytes), endocrine (TSH, serum calcium, parathyroid hormones), serum lithium estimations (trough). Lithium should be carefully monitored due to potential for toxicity (Wilting et al., 2005; Lam et al., 2009).	Obesity, metabolic syndrome, hypertension, and diabetes. Small increased risk of fetal cardiac defects (Cohen et al., 1994; McKnight et al., 2012; Diav-Citrin et al., 2014). Recommend treatment with thyroid hormone if hypothyroidism occurs. Cautioned that long-term use associated with serious side effects (Van and Boer, 2006; Malhi et al., 2012).	–
TMAP	300 mg/d titrated by 150 mg/d every 1/2 wk to target dose 600–900 mg/d. Max. based on serum levels considered with tolerability and response, aiming for 0.4–0.6 mmol/L 1–2 times p/d.	ECG at baseline and yearly as indicated. FBC baseline and yearly. TFTs at baseline, TSH every 6 mo/ as indicated. BUN at baseline and as indicated (including creatine, glucose, and electrolytes). Urinalysis at baseline and as indicated. Pregnancy test if indicated. Lithium levels 1-wk post initiation, after each change in dose, and as clinically indicated.	Acne, acute renal dysfunction, cognition, diarrhea, dizziness, ECG changes, GI upset, hypothyroidism, nausea, polyuria, sedation, thirst, tremor, and weight gain	ACE inhibitors, caffeine, NSAIDs, osmotic diuretics, theophylline, and thiazide diuretics
WFSBP	Trough (12 h post) serum levels 0.6–0.8 mmol/L in acute and maintenance phase. 0.4–1.0 mmol/L may be appropriate depending on response and tolerability. Translates to approximately 900–1200/1500 mg/d lithium carbonate. Single daily dose may increase adherence and reduce side effects (Mosolov et al., 1997). XR formulation better tolerated. Acknowledged that optimal levels may vary (Schou, 1989; Malhi et al., 2011). Specific recommendations made for Asian and elderly populations.	Serum test no earlier than 5–7 days after first dose/ changes in dose, 1–4/y, more if indicated. 1–2/y: TFTs, parathyroid function (e.g., blood calcium, and if this is elevated, parathyroid hormone), and renal function (eGFR, creatine; Schou et al., 1997; Livingstone and Rampes, 2006; American Psychiatric Association, 2010; Berger et al., 2013; Severus and Bauer, 2013; Bschor, 2014). Response assessed 2–4 wk post initiation. Monitor for response from 2 to 4 wk (Bschor et al., 2003).	Potential for serotonin syndrome when MAOI/other AD augmented with lithium. Reduced GFR, reduced urinary concentrating ability, polyurea and/or polydipsia, goiter and hypothyroidism, hyperparathyroidism, weight gain, GI symptoms, memory impairment or mental slowness (McKnight et al., 2012). Some patients receiving lithium for ≥10 y may develop rising creatine concentrations, but glomerular and tubular function more commonly affected (Bendz et al., 2010). Hand tremor. Side effects often dose dependent. See guidelines for guidance on how to counteract side effects.	–

Abbreviations: –, not reported by guideline; AAPs, atypical antipsychotics; ACE, angiotensin-converting enzyme; AD, antidepressant; APA, American Psychiatric Association; BAP, British Association of Psychopharmacology; BUN, blood urea nitrogen; CANMAT, Canadian Network for Mood and Anxiety Disorders; CPG-S, Clinical Practice Guidelines in the Spanish NHS; CVD, cardiovascular disease; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; FBC, full blood count; GI, gastrointestinal; ICSI, Institute for Clinical Systems Improvement; MAOI, monoamine oxidase inhibitors; mg/d, milligrams per day; mmol/L, millimoles per litre; MPG, Maudsley Prescribing Guideline; NICE, National Institute for Health and Care Excellence; NMS, neuroleptic malignant syndrome; p/d, per day; NSAID, non-steroidal anti-inflammatory drug; QT, Q-T interval; RANZCP, Royal Australian and New Zealand College of Psychiatrists; TCAs, tricyclic antidepressants; TFTs, thyroid function tests; TMAP, Texas Medication Algorithm Project; TSH, thyroid stimulating hormone; WFSBP, World Federation of Societies of Biological Psychiatry; XR, extended release.

Table 13. Summary of Lithium Discontinuation Guidance

Guideline	Discontinuation guidance
APA	If tolerated and effective, treatment should continue for at least an acute phase (typically 4–8 wk) and potentially beyond for relapse prevention.
BAP	Lithium should be maintained in combination with an antidepressant for at least 1 y to prevent relapse, though little available evidence in continuation phase. Routine use of lithium monotherapy in continuation phase not recommended. Supported their recommendations with conflicting evidence demonstrating that lithium had nonsignificant benefit over placebo or antidepressants for prophylaxis (Burgess et al., 2001; Cipriani et al., 2006), but lithium plus an antidepressant more effective than antidepressant monotherapy in preventing relapse in TRD patients who responded to lithium augmentation or ECT (Bauer et al., 2000; Sackeim et al., 2001).
CANMAT	–
CPG-S	–
ICSI	Care should be taken when discontinuing lithium as abrupt withdrawal associated with higher relapse rates
MPG	Advised against lithium monotherapy for prophylaxis. At least 2 y continuation in patients with ≥2 recent episodes with significant functional impairment, then reevaluate. If first episode, continue for 6–9 mo following remission. Following noncompliance, recommence at previous dose if adherence and tolerance good (Abou-Saleh et al., 2017a). Treatment should be indefinite if adherence good and treatment well tolerated, particularly if suspected bipolarity. Few data relating to lithium discontinuation in unipolar depression. Should be reduced slowly over at least 1 mo, avoiding incremental reductions >0.3 mmol/L in recurrent depression. Referred to work that proposed lithium should be used for prophylaxis in depression if had been 2 depressive episodes in 5 y or following 1 severe episode with strong suicide risk (Abou-Saleh et al., 2017b).
NICE	Responders with multiple historical relapses should remain on medication regardless of length of treatment pre-response. Insufficient evidence to determine effect beyond 2 y or if relevant to first-episode patients. If a medication to be stopped, it should be the augmenter not AD. Relapse likelihood lower if lithium continued (Prien et al., 1984). Not enough evidence to determine clinically important difference between continuing lithium as monotherapy or discontinuing both lithium and AD (i.e., placebo).
RANZCP	Care should be taken when discontinuing lithium as abrupt withdrawal associated with higher relapse rates (Bschor et al., 1999). Lithium monotherapy in maintenance phase could be considered if ADs not well tolerated (Cipriani et al., 2006).
TMAP	–
WFSBP	Continuation for at least 1 y if patient responds. Gradual withdrawal tapered over at least 3 mo if treatment has been >6 mo. If symptoms reoccur, maintenance dose of antidepressant and lithium should be resumed. Recommended administration for 2–4 wk and then monitor patient response (Bschor et al., 2003). Efficacy of lithium maintenance treatment well established (Coppen et al., 1990; Schou, 1997; Davis et al., 1999; Bauer et al., 2000; Paykel, 2001; Bschor et al., 2002). Evidence for lithium monotherapy in prophylaxis not sufficient (Souza and Goodwin, 1991; Burgess et al., 2001), but more recent meta-analysis showed efficacy of lithium when used for preventative purposes, though relative efficacy was not (Cipriani et al., 2006). Lithium + AD in continuation phase more beneficial than antidepressant + placebo, AD monotherapy, or lithium monotherapy (Kim et al., 1990; Bauer et al., 2000; Bschor et al., 2002). Stopping lithium can lead to relapse or recurrence.

Abbreviations: –, not reported by guideline; AD, antidepressant; AAPs, atypical antipsychotics; APA, American Psychiatric Association; BAP, British Association of Psychopharmacology; CANMAT, Canadian Network for Mood and Anxiety Disorders; CPG-S, Clinical Practice Guidelines in the Spanish NHS; ECT, electroconvulsive therapy; ICSI, Institute for Clinical Systems Improvement; MPG, Maudsley Prescribing Guidelines; NICE, National Institute for Health and Care Excellence; RANZCP, Royal Australian and New Zealand College of Psychiatrists; TMAP, Texas Medication Algorithm Project; WFSBP, World Federation of Societies of Biological Psychiatry.

Barbee et al., 2011) and stated that there is insufficient data to recommend augmentation with lamotrigine, carbamazepine, valproate, or topiramate.

ISCI, RANZCP, and WFSBP did not discuss augmentation with any mood stabilizer/anticonvulsant other than lithium for unipolar resistant depression.

Dosage

The MPG stated that 100, 200, or 400 mg/d has been used for adjunct lamotrigine, though this was not clearly a recommendation. TMAP offered the most comprehensive guidance for lamotrigine, recommending 25 mg/d for 2 weeks, increased to 50 mg/d for 2 weeks, then 100 mg/d for 1 week, with a maximum daily dose of 200 mg/d in the absence of enzyme inhibiting or inducing agents. TMAP offered slightly different guidance for patients taking carbamazepine or valproate in addition to lamotrigine. No other guidelines included dosage recommendations.

Side effects and monitoring

TMAP did not discuss side effects but recommended that renal function and hepatic function tests should be conducted prior to lamotrigine treatment and repeated yearly if indicated. A pregnancy test was also recommended if appropriate. TMAP stated that their recommendations were supported by Level B evidence but did not directly cite this work.

Discontinuation

BAP recommended that lamotrigine should be continued for up to 1 year after remission, with long-term treatment considered for higher risk patients. The MPG and TMAP did not offer specific withdrawal guidance, but as TMAP is algorithmic, further treatment is recommended should a patient not/partially respond. The MPG listed lamotrigine as a treatment that would require re-titration after 3 to 7 days of noncompliance. No other discontinuation guidance was provided for this group of treatments in unipolar depression.

Bupropion

Although licensed as an antidepressant in some countries, including the United States, bupropion is specifically listed as an augmenter in others and is therefore included as such in this review. The following section therefore only includes mention of bupropion as an antidepressant adjunct.

First-line recommendations

The MPG listed bupropion as a first-line augmenter for TRD, added to an SSRI. They stated that bupropion use as a "worthwhile" option is supported by STAR*D (Trivedi et al., 2006a) but highlighted that it is not licensed for use in depression in the United Kingdom (Fatemi et al., 1999; Pierre and Gitlin, 2000; Lam et al., 2004; Papakostas et al., 2006b; Zisook et al., 2010; Henssler et al., 2016).

TMAP initially recommended bupropion as an augmenter at stage 1A (for patients with a partial response to initial antidepressant treatment), then at stage 2A, stages 3, 3A, 4, and stages 6–8.

Second-line recommendations

CANMAT recommended bupropion as a second-line augmenter with Level 2 evidence, which included the network meta-analysis previously mentioned in which bupropion was not significantly more effective than placebo (Zhou et al., 2015).

Other recommendations

BAP listed bupropion as "other additions that could be considered" with level B evidence. APA stated that the addition of bupropion to an antidepressant is supported by limited evidence and clinical experience, citing a study in which an SSRI plus bupropion had better outcomes than SSRI or bupropion monotherapy, as per the APA (Lam et al., 2004). The BAP and APA also listed special populations in which bupropion may be an appropriate choice.

ICSI included bupropion in combination with an SSRI (recommendations not ranked). The STAR*D study was referenced (as in the MPG), indicating no significant difference between bupropion and buspirone augmentation of citalopram, though bupropion was better tolerated (Trivedi et al., 2006a). They also referred to several case series/case reports of bupropion augmentation that described beneficial results (Marshall and Liebowitz, 1996; Bodkin et al., 1997; Spier, 1998).

Not recommended

RANZCP and WFSBP did not recommend the use of bupropion as an augmentation (or combination) strategy for TRD, though both listed it as an antidepressant. WFSBP referenced the STAR*D comparison of bupropion and buspirone augmentation (Trivedi et al., 2006a), but in contrast to other guidelines, referred specifically to a secondary modified intention to treat analysis, including only participants with data from at least 1 follow-up visit, in which buspirone was less effective than bupropion (Bech et al., 2012).

The CPG-S and NICE did not include bupropion as an augmentation option. Both mentioned the STAR*D study in which buspirone and bupropion augmentation did not differ significantly in terms of efficacy (Trivedi et al., 2006b), though NICE highlighted that there was a greater reduction in self-rated depression severity for the bupropion group. NICE also noted that dropout due to side effects was lower in the bupropion group.

Dosage, side effects, and monitoring

See Table 14 for dosage, side effect, and monitoring recommendations for bupropion provided by the guidelines.

Discontinuation

The MPG advised that bupropion discontinuation symptoms, similar to those associated with SSRI use, have been documented in a few cases, but this was not specific to its use as an augmenter (Berigan and Harazin, 1999; Berigan, 2002). No other included guidelines included discontinuation advice for bupropion.

Buspirone

First-line recommendations

TMAP included buspirone augmentation at stage 1a and 2a of their algorithm, meaning it can be considered a first-line option. TMAP did not cite the evidence used.

Second-line recommendations

The MPG listed buspirone as a second-line augmenter when added to an SSRI. The STAR*D comparison with bupropion was again referenced (Trivedi et al., 2006b), though the MPG guarded that the need for a higher dose and poor tolerability are disadvantages (Appelberg et al., 2001; Trivedi et al., 2006b).

Other recommendations

The ICSI listed buspirone as an augmentation method for use in combination with an SSRI. They also referenced the STAR*D comparison with bupropion (Trivedi et al., 2006b) plus 2 case series/chart reviews reporting beneficial results (Bouwer and Stein, 1997; Dimitriou and Dimitriou, 1998).

APA recommended buspirone augmentation with its third level of confidence (recommended based on individual circumstances) for TRD patients with prominent features of anxiety and/or insomnia. A different STAR*D study was discussed in which CBT augmentation was reported to be as effective as buspirone add-on, bupropion add-on, or an antidepressant switch (Thase et al., 2007b). APA also noted the STAR*D comparison of buspirone and bupropion augmentation, and though both were associated with remission rates of approximately 30%, APA highlighted that bupropion was superior on a number of secondary outcomes (Trivedi et al., 2006b).

BAP included buspirone augmentation under "other additions that could be considered" (level B evidence). They stated that the evidence is less robust than for lithium, quetiapine, risperidone, and aripiprazole, and buspirone was not as well tolerated and marginally less effective than bupropion (Trivedi et al., 2006b). The BAP mentioned 2 other studies in which buspirone augmentation was not effective (Landen et al., 1998), though a beneficial effect was found in the more severely depressed patients (Appelberg et al., 2001).

Not recommended

The WFSBP guidelines did not recommend buspirone augmentation, referring to a narrative review by (Connolly and Thase, 2011) and 2 placebo-controlled RCTs (Landen et al., 1998; Appelberg et al., 2001). As discussed, they also referred to the STAR*D comparison with bupropion (Trivedi et al., 2006b), highlighting the modified intention to treat analysis in which buspirone was less effective (Bech et al., 2012).

Similarly, RANZCP advised that the evidence for buspirone augmentation is unconvincing, citing only the 2009 CANMAT

Table 14. Bupropion Monitoring and Dosing

Guideline	Dose	Patient monitoring parameters	Specific side effects	Specific drug interactions
APA	150 mg/d titrated up to 300–450 mg/d (for IR and XR formulations). Suggested dosage in morning for activation purposes and to avoid insomnia. Advised taking after food or in divided doses if experiencing nausea/vomiting.	Blood pressure (association with hypertension)	Dry mouth, headaches, tremors, agitation, jitteriness, mild cognitive dysfunction, insomnia, and GI symptoms (Fava et al., 2005a). May improve symptoms of sleepiness and fatigue in some (Papakostas et al., 2006a). Can reduce seizure threshold and should be used with caution/avoided in those with preexisting seizure disorders/at risk of seizure. Bupropion should not be used in patients with anorexia nervosa or bulimia nervosa for this reason (American Psychiatric Association, 2006). Potential dopamine agonist effects may be beneficial for symptoms of Parkinson's but could worsen psychosis. Relatively safe in overdose. As an antidepressant, bupropion does not have an indication for anxiety, and therefore clinicians may want to avoid use in these patients. Patients typically have weight loss or only minimal weight gain with bupropion; may be helpful for smoking cessation (Kleber et al., 2007; Hughes et al., 2014). Noted lack of data examining bupropion's effect on pregnancy. Can help with sexual side effects of other ADs (Walker et al., 1993; Clayton et al., 2004).	Risk of seizure may be increased if bupropion prescribed with inhibitors of CYP 2D6, such as desipramine, sertraline, paroxetine, and fluoxetine, as this can increase blood levels of bupropion
BAP	No general dose recommendations but commented on a study (n = 3000) that reported better adherence with once-daily rather than twice-daily dosing (McLaughlin et al., 2007).	–	Insomnia/agitation, increased seizure potential, and QTc shortening (Castro et al., 2013a)	Moderate inhibitor of CYP2D6 (Spina et al., 2008), so advised seeking specialist advice if concerns about such interactions
CANMAT	150–300 mg/d. Specific dosing advice for patients experiencing sexual dysfunction	–	–	–
CPG-S	Not recommended			
ICSI	–	–	–	–

Table 14. Continued

Guideline	Dose	Patient monitoring parameters	Specific side effects	Specific drug interactions
MPG	Up to 400 mg/d, or 300 mg for XR formulation. Specific advice for patients with renal impairment. Mentioned alternative formulations (e.g., buccal) but no dosing information (Almeida et al., 2015).	Blood pressure. Patients with renal impairment should be monitored for urinary retention, confusion, sedation, and postural hypotension, and suggested plasma level or ECG monitoring may prove useful.	Potential cardiac effects: slight increase in heart rate, increase in blood pressure that can sometimes be significant, rare postural hypotension, QTc shortening (although QTc prolongation has been reported in overdose; Paris and Saucier, 1998; Buckley and Faunce, 2003; Curry et al., 2005; Zhu et al., 2017), rare reports of arrhythmia in overdose. Potential for MI (Roose and Miyazaki, 2005; Dwoskin et al., 2006; Castro et al., 2013b; Eisenberg et al., 2013). Not indicated in patients with eating disorders, alcohol dependence, or seizure disorder. Can be pro-convulsive, particularly in IR formulation. Common adverse effects include: dizziness, taste changes, GI disturbance, concentration problems, tremor, and insomnia. Association between bupropion and prolactin, but single doses up to 100 mg do not appear to affect (Whiteman et al., 1982). Low risk of hyponatremia (Kate et al., 2013). Moderate toxicity in overdose: lowest dose likely to be fatal approximately 4.5 g, though there is evidence of a 13.5-g overdose that was not fatal (Zhu et al., 2016). Signs of overdose include tachycardia, arrhythmia, QTc and QRS prolongation, and seizures (Paris and Saucier, 1998; Buckley and Faunce, 2003; Curry et al., 2005; Mercerolle et al., 2008).	Caution advised when co-administered with medications known to induce or inhibit cytochrome CYP2B6 metabolism as clinical efficacy may be impacted. Administration alongside other drugs metabolised by this pathway should be avoided.
NICE	Not recommended			
RANZCP	Not recommended			
TMAP	75–150 mg/d with max 400 mg/d for standard release, taken twice daily or 450 mg in XR formulation once daily. Both generic and branded (Wellbutrin) versions available.	Pregnancy test if indicated and monitoring for emergence of suicidal ideation/behavior	Constipation, dry mouth, headaches, insomnia, nausea, and seizures	Phenelzine, tranylcypromine, selegiline, carbamazepine, cyclosporine, linezolid, MAOIs, ritonavir, and TCAs also listed
WFSBP	Not recommended			

Abbreviations: –, not reported by guideline; ADs, antidepressants; APA, American Psychiatric Association; BAP, British Association of Psychopharmacology; CANMAT, Canadian Network for Mood and Anxiety Disorders; CBT, cognitive behavioural therapy; CPG-S, Clinical Practice Guidelines in the Spanish NHS; ICSI, Institute for Clinical Systems Improvement; IR, immediate release; MI, myocardial infarction; MOAI; monoamine oxidase inhibitors; MPG, Maudsley Prescribing Guidelines; NICE, National Institute for Health and Care Excellence; QT, Q-T interval; QRS, QRS complex; RANZCP, Royal Australian and New Zealand College of Psychiatrists; TCAs, tricyclic antidepressants; TMAP, Texas Medication Algorithm Project; WFSBP, World Federation of Societies of Biological Psychiatry; XR, extended release.

Table 15 Buspirone Monitoring and Dosing

Guideline	Dose	Monitoring	Specific side effects	Specific drug interactions
APA	–	–		Cautioned against augmenting MAOIs with buspirone, including reversible inhibitors of monoamine oxidase and selegiline, due to risk of serotonin syndrome (Sternbach, 1991; Boyer and Shannon, 2005; Stahl and Felker, 2008)
BAP	–	–	–	–
CANMAT	Not recommended			
CPG-S	Not recommended			
ICSI	–	–	–	–
MPG	Up to 60 mg/d. Specific advice for renal impairment		Nausea, dizziness and headaches. Manufacturer contraindicates use in patients with severe renal impairment (Aronoff et al., 2007; Ashley and Currie, 2008).	
NICE	Not recommended			
RANZCP	Not recommended			
TMAP	Starting dose 15 mg/d, increased every week by 15 mg/d until target dose of 20–60 mg/d (max 60 mg/d) reached. Dose should be divided and taken 2–3 times throughout day.	Pregnancy test as indicated.	Dizziness, drowsiness, headache and nausea	Alcohol, furazolidone, MAOIs, SNRIs, SSRIs, and grapefruit juice
WFSBP	Not recommended			

Abbreviations: –, not reported by guideline; APA, American Psychiatric Association; BAP, British Association of Psychopharmacology; CANMAT, Canadian Network for Mood and Anxiety Disorders; CPG-S, Clinical Practice Guidelines in the Spanish NHS; ICSI, Institute for Clinical Systems Improvement; MAOI, monoamine oxidase inhibitor; MPG, Maudsley Prescribing Guidelines; NICE, National Institute for Health and Care Excellence; RANZCP, Royal Australian and New Zealand College of Psychiatrists; SNRI, serotonin-norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; TMAP, Texas Medication Algorithm Project; WFSBP, World Federation of Societies of Biological Psychiatry.

Table 16. Thyroid Hormone Dosage and Monitoring

Guideline	Dose	Patient monitoring parameters	Specific side effects	Specific drug interactions
APA	25 mcg/d increased to 50 mcg/d after ~1 wk if response inadequate	–	–	–
BAP	–	–	–	–
CANMAT	25–50 mcg	–	–	–
CPG-S	Not recommended	Not recommended	Not recommended	Not recommended
ICSI	Usual doses of T3 vary between 25 and 50 mcg/d (Nelson, 2000)	–	–	–
MPG	20–50 mcg/d but higher doses have been safely used	Clinical and biochemical TFT monitoring required. T3 augmentation would usually need specialist referral.	–	–
NICE	Not recommended	Not recommended	Not recommended	Not recommended
RANZCP	–	Monitored in same way as patients with Hypothyroidism: TSH, T3, and free T4 levels measured regularly (Rosenthal et al., 2011)	–	–
TMAP	–	Thyroid function test at baseline and as clinically indicated	Most common side effects are diarrhea, headache, irritability, nervousness, sweating, and tachycardia	Anticoagulants, hypoglycemics, oral contraceptives, TCAs
WFSBP	Advised that most studies dosed at 25–37.5 mcg/d and referred to Łojko and Rybakowski (2007) for T4	–	Should be prescribed with caution due to potential adverse effects (not detailed)	–

Abbreviations: –, not reported by guideline; APA, American Psychiatric Association; BAP, British Association of Psychopharmacology; CANMAT, Canadian Network for Mood and Anxiety Disorders; CPG-S, Clinical Practice Guidelines in the Spanish NHS; ICSI, Institute for Clinical Systems Improvement; MPG, Maudsley Prescribing Guidelines; NICE, National Institute for Health and Care Excellence; RANZCP, Royal Australian and New Zealand College of Psychiatrists; T3, triiodothyronine; T4, thyroxine; TCAs, tricyclic antidepressant; TMAP, Texas Medication Algorithm Project; TSH, thyroid stimulating hormone WFSBP, World Federation of Societies of Biological Psychiatry.

guidelines (Lam et al., 2009). The current CANMAT guidelines briefly mentioned buspirone augmentation in relation to the network meta-analysis by Zhou and colleagues (2015), in which it was not more effective than placebo (Zhou et al., 2015).

NICE stated that there is insufficient evidence to recommend buspirone or determine if there is a clinically significant difference between SSRI monotherapy and buspirone augmentation. They advised that there was no evidence from double-blind, placebo-controlled studies at the time of publication. NICE also commented that at the time of writing, the United Kingdom did not have marketing authorization for this indication. Again, STAR*D was highlighted, as dropout was greater in patients taking buspirone compared with bupropion augmentation (Rush et al., 2003).

The CPG-S guidelines did not include buspirone in their recommendations.

Dosage, monitoring, and adverse effects

See Table 15.

Discontinuation

None of the included guidelines offered any discontinuation advice for buspirone augmentation.

Thyroid Hormones

First-line recommendations

TMAP recommended thyroid augmentation at both stage 1a and 2a of their algorithm. They did not cite the evidence to support these recommendations.

RANZCP included T3 as a Level I augmenter but noted that the results from clinical studies are inconsistent and thyroxine (T4) has been less widely assessed, though they found it reasonable to extrapolate the findings. RANZCP emphasized the mixed evidence for T3, highlighting a 2008 review (Cooper-Kazaz and Lerer, 2008), but advised that T3 augmentation should be used in those with and without subclinical hypothyroidism.

Second-line recommendations

CANMAT recommended T3 as a second-line augmenter supported by Level II evidence. As discussed, CANMAT referred to the network meta-analysis by Zhou et al. (2015) that reported T3 to be more effective than placebo. Despite this, they stated that there is insufficient evidence to recommend T3 as a first-line augmenter given that there have been no additional placebo-controlled RCTs since the 2008 review also mentioned by RANZCP, which identified only 2 (Cooper-Kazaz and Lerer, 2008). CANMAT also referred to the STAR*D trial (Nierenberg et al., 2006), noting that although there was no difference in remission rates between lithium and T3 augmentation, T3 was better tolerated.

WFSBP listed both T3 and T4 as second-line strategies but acknowledged that studies had largely focused on T3, and high-quality evidence remains sparse. WFSBP stated that the evidence base for T3 consisted of many case series and 13 prospective trials at the time of publication (9 open-label and 4 double-blind RCTs) and most augmented TCAs in TCA nonresponders (Joffe et al., 1993; Altshuler et al., 2001; Bauer and Whybrow, 2001). They noted that not all controlled double-blind studies significantly favored T3 vs placebo and highlighted the same meta-analysis as RANZCP (Aronson et al., 1996). They also mentioned the STAR*D comparison with lithium (Nierenberg et al., 2006). For T4, WFSBP reported a small number of studies (open-label) with response rates of approximately 50% for TRD patients using higher, supra-physiological doses (Bauer et al., 1998, 2002a).

The MPG listed T3 as a second-line option, mentioning evidence of good tolerability and citing STAR*D (Nierenberg et al., 2006). They highlighted that there are some negative studies (not referenced) and suggested that manufacturer monopoly may result in a high purchase cost for some counties.

APA recommended thyroid hormone augmentation with "moderate clinical confidence," referring to evidence that it may increase antidepressant efficacy, again including STAR*D (Aronson et al., 1996; Nierenberg et al., 2006). APA did not mention T4 augmentation. BAP similarly recommended T3 as second-line (class B). BAP cited both the meta-analysis referenced by APA (Aronson et al., 1996) and the STAR*D study (Nierenberg et al., 2006) but stated that the meta-analysis included just 4 small RCTs, and while a significant improvement in HDRS scores was reported with T3, there was a nonsignificant difference in response rates. BAP also noted that lithium levels were not consistently monitored in STAR*D, and referenced 1 additional study, which although small, reported no difference between augmentation with T3, lithium, or placebo over 2 weeks (Joffe et al., 2006). BAP did not include T4 augmentation.

Other recommendations

ICSI included T3 augmentation as an option but did not specify the level of confidence. Again, STAR*D was referenced, indicating that T3 is better tolerated than lithium (Nierenberg et al., 2006), but the ICSI mentioned that placebo-controlled trials have found mixed results. There was no discussion of T4 augmentation.

Not recommended

NICE did not include T3 in their clinical practice recommendations due to a lack of evidence and advised that it should not be used routinely. They commented that existing studies predominantly assessed TCA augmentation (Altshuler et al., 2001), with STAR*D being the only evidence of efficacy with SSRIs at the time of publication (Nierenberg et al., 2006). NICE suggested that response rates have been variable across studies for thyroid hormone augmentation (Aronson et al., 1996) and referred to just 1 RCT in which there was a significant difference between T3 and placebo for response, but not the reduction of depressive symptoms (Joffe et al., 1993). NICE also noted 1 study in which T4 was inferior to T3 (Joffe and Singer, 1990) but made no recommendations for T4. NICE stated that there was no evidence regarding treatment acceptability for thyroid hormone augmentation, and thyroid hormones did not have UK marketing authorization for augmentation at the time of publication. They advised clinicians to obtain documented informed consent for this option.

Similarly, CPG-S (referring to NICE) advised there is not enough evidence to recommend augmentation with thyroid hormones. CPG-S drew on a study comparing a range of augmenters that found no significant difference between T3 and any other (Fang et al., 2011). Again the STAR*D study was referenced (Nierenberg et al., 2006) as was Joffe et al. (1993).

Dosage, side effects, and monitoring

See Table 16 for dosage, side effect, and monitoring recommendations for thyroid hormones provided by the guidelines.

Discontinuation guidance

None of the guidelines included discontinuation advice for thyroid hormone augmentation.

Stimulants

Second-line recommendations

CANMAT recommended modafinil as a second-line adjunctive agent citing a meta-analysis of 4 MDD RCTs (Goss et al., 2013).

Other recommendations

APA recommended modafinil as an additional strategy for cases of antidepressant nonresponse but cautioned that there is less evidence for efficacy than for other treatments (evidence level III: recommended based on individual circumstances only). Despite this, APA highlighted modafinil as the best treatment for fatigue and hypersomnolence when combined with an SSRI, based on 4 studies (DeBattista et al., 2003a; Ninan et al., 2004; Dunlop et al., 2007; Fava et al., 2007). APA also advised that methylphenidate or dextroamphetamine may be useful (Masand et al., 1998; Lavretsky et al., 2006; Ravindran et al., 2008) but cautioned that not all clinical trials have shown benefits (Patkar et al., 2006).

The MGP featured modafinil in their "other reported treatments" section due to the lack of evidence supporting its use as an adjunctive treatment (Fawcett et al., 1991; DeBattista et al., 2004; Lavretsky et al., 2006; Taneja et al., 2007) and stated that other augmentation options are better supported, as the evidence for stimulants (methylphenidate, dexamfetamine, and lisdexamfetamine) is generally inconclusive and inadequate (Fawcett et al., 1991; Parker and Brotchie, 2010; Trivedi et al., 2013; Madhoo et al., 2014; Israel, 2015). In line with APA, the MPG recommended modafinil for patients experiencing fatigue but acknowledged that these effects are not clearly understood (DeBattista et al., 2003b; Fava et al., 2005b).

The guidance from BAP regarding modafinil augmentation is limited, as they stated that there is only preliminary evidence for its use over the short term and cited the same meta-analysis of 4 MDD RCTs as CANMAT (Goss et al., 2013). They concluded the evidence to be Level C (potentially including nonexperimental, descriptive studies). BAP also suggested that modafinil may improve sleepiness but, like the MPG stated that this effect is unclear and cited similar research to APA (Fava et al., 2007).

The ICSI recommended modafinil in addition to a TCA or SSRI, calling this a "jump-start response" and citing open-label studies demonstrating benefit for sleepiness and fatigue (Ninan et al., 2004; Schwartz et al., 2004). They highlighted the need for larger, higher quality RCTs to establish the benefit of stimulant augmentation (Fava et al., 2005b; Dunlop et al., 2007; Candy et al., 2008) and reported cases of sudden death, stroke, and myocardial infarction in adults taking doses recommended for attention deficit hyperactivity disorder. ICSI cautioned against prescribing in those with cardiac problems.

Not recommended

RANZCP stated that there was insufficient evidence of efficacy and so did not recommend stimulant augmentation, as did NICE. However, NICE referenced other sources for details about these strategies, including the 2002 WFSBP guidelines (Thase and Rush, 1997; Bauer et al., 2002b).

Neither modafinil nor any other stimulant featured in the CPG-S, TMAP, or WFSBP.

Dosage

The MGP and CANMAT recommended 100–400 mg/d of modafinil added to an antidepressant. APA recommended low doses of stimulants such as methylphenidate or dextroamphetamine, and the MPG advised 7.5–40 mg dexamfetamine or 50 mg of lisdexamfetamine when combined with an MAOI, 20–50 mg of lisdexamfetamine when combined with escitalopram, and 20–30mg of lisdexamfetamine when combined with another antidepressant. APA and BAP did not include dosage guidelines for stimulant augmentation.

Side effects and monitoring

Although APA did not explicitly advise on pre-prescription and monitoring tests for modafinil, they advised that clinicians should be aware of Stevens-Johnson syndrome and other cutaneous reactions, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms, and cytochrome P450 interactions. They also advised that modafinil can induce CYP 3A4 and render contraceptive and other medications metabolized through this route ineffective. APA also stated that stimulants should be added to MAOIs only with extreme caution (Feighner et al., 1985; Fawcett et al., 1991).

BAP recommended that modafinil should only be prescribed in specialist centers with careful monitoring, and the MPG cautioned that modafinil augmentation may worsen anxiety symptoms. No pre-prescribing or monitoring checks were reported for any other stimulant.

Discontinuation

The BAP, MPG, and CANMAT offered no discontinuation/withdrawal advice for modafinil. APA cited 1 study in which the effects of modafinil were maintained over 12 weeks (Fava et al., 2007), but it was not clear whether this was a recommended treatment length. The MPG included stimulants among the treatments that are "probably" safe to recommence at the previous dose following noncompliance.

Ketamine

Second-line recommendations

The MPG listed i.v. ketamine as a second-line augmenter and highlighted the potential for this to be superseded by its intranasal form in the near future (Daly et al., 2018). They also cited studies of intramuscular and subcutaneous administration, sublingual administration, and transmucosal routes (Lara et al., 2013; Nguyen et al., 2015; Loo et al., 2016). They discussed the very rapid response rates and high short-term remission rates and mentioned evidence of maintained response if repeated doses are administered (not referenced). The MPG stated that ketamine is usually well tolerated. However, the need for i.v. ketamine to be administered in hospital and poor availability were disadvantages.

Other recommendations

The ICSI listed ketamine infusion therapy a specialized treatment. They reviewed the evidence base for the antidepressant properties of ketamine (Aan Het Rot et al., 2012; Fond et al., 2014a) but stated that more research is required before recommendation of its use in standard clinical settings, especially studies evaluating long-term response and with larger sample sizes.

CANMAT recommend ketamine as an experimental adjunctive agent in an academic setting but echoed caution against adverse reactions, potential abuse, and its efficacy long term (Fond et al., 2014b; Serafini et al., 2014a; Coyle and Laws, 2015; Wan et al., 2015).

Not recommended

RANZCP, BAP, and WFSBP did not recommend ketamine augmentation. RANZCP and the BAP both considered a study by Murrough and colleagues (2013) as evidence for its success as a short-term treatment (Murrough et al., 2013) and highlighted potential adverse events and toxicity (Price et al., 2009; Zarate et al., 2012; Serafini et al., 2014b). The WFSBP recognized the growing interest in glutamatergic agents but concluded that there is insufficient evidence.

TMAP, APA, NICE, and CPG-S did not mention ketamine augmentation. NICE reasoned that the evidence base at the time of publication was too weak and clinical usage too low; however, they did refer readers to alternative sources should they wish to know more.

Dosage

The MPG listed a dose of 0.5 mg/kg over 40 minutes in its i.v. form. The BAP advised that optimal dosing was not yet established.

Monitoring and adverse effects

The MPG mentioned that cognitive side effects (e.g., confusion and dissociation) usually occur with ketamine augmentation and that it is associated with a temporary increase in blood pressure, tachycardia, and arrhythmias. The MPG acknowledged that the adverse effects associated with ketamine may be underestimated in the literature (Short et al., 2018), and advised a pretreatment ECG (Aan het Rot et al., 2010). The ICSI and CANMAT did not offer side effect and monitoring advice.

Discontinuation

None of the included guidelines specifically discussed the discontinuation of ketamine augmentation, which remains relevant even in its i.v. form, as some of the studies discussed by the guidelines (e.g., the ICSI) included multiple doses (Szymkowicz et al., 2013).

Discussion

This review provides a comprehensive overview of treatment guidelines for pharmacological augmentation in unipolar depression, to aid clinicians in their provision of evidence-based care, support researchers in their identification of research needs, and guide the development of future guidelines and guideline updates.

Recommended Treatments

Lithium was the only agent to be recommended across all 10 guidelines and is the most widely studied pharmacological augmenter in patients who have not responded to 2 or more antidepressants (Strawbridge et al., 2019). None of the 4 North American guidelines recommended lithium as a first-line option, while 5 others did, indicating geographical differences in preference. Concerningly, the reason for this was not made apparent by the guidelines but may reflect the fact that lithium is not approved for use in unipolar TRD in the United States.

AAPs were also recommended by all 10 guidelines, though no single agent was clearly universally endorsed. Aripiprazole was the most widely recommended, broadly in line with existing meta-analytic evidence demonstrating aripiprazole to be the most widely studied AAP in TRD (Strawbridge et al., 2019) and to have the most robust evidence base, along with quetiapine (Zhou et al., 2015). All guidelines published from 2015 onwards (the date of the most recent AAP RCT included by Strawbridge et al., 2019) recommended aripiprazole as a first-line option, bar the ICSI who did not rank their recommendations. Risperidone, olanzapine, and quetiapine were also recommended by the majority, though just 1 RCT examining treatment efficacy was identified for each by Strawbridge et al. (2019). However, previous reviews have also identified atypical antipsychotics as the best supported pharmacological augmentation options for TRD (McIntyre et al., 2014).

Less consistency was found for all other augmenters. The BAP, MPG, TMAP, and APA made recommendations for anticonvulsant mood stabilizers (primarily lamotrigine), while NICE, CANMAT, and the CPG-S advised against their use due to a lack of evidence. This cannot be accounted for by variation in guideline publication date or licensing and instead indicates differences in evidence interpretation and perhaps guideline quality, though there was not a clear split according to AGREE II scores (Table 2). The ICSI, RANZCP, and WFSBP also failed to mention anticonvulsant mood stabilizers, and the CPG-S, TMAP, and WFSBP did not mention stimulants. While it is plausible that guidelines will have some differences in their interpretation of the evidence, stark inconsistencies reduce clarity and may mean that the treatment options available to a patient are somewhat dependent on the guideline used by their clinician rather than the full range of evidence based options available, which may in some cases be problematic. Clinicians may therefore wish to consult multiple guidelines and use this review to identify the most appropriate guidance for their needs.

There were clear differences in recommendations for bupropion and buspirone, some of which can be attributed to bupropion's status as a licensed antidepressant in North America, but not Europe/Australasia. Most guidelines referred to the STAR*D comparison of bupropion and buspirone augmentation yet used it to support contrasting advice (e.g., the CPG-S and NICE did not recommend bupropion and buspirone, while the APA, MPG, and ICSI did) (Trivedi et al., 2006b). CANMAT was the only guideline to use the recent Zhou network analysis to support their recommendations despite the MPG and ICSI having later dates of publication. Clearly there is a need for greater alignment between guidelines in terms of their grading of available evidence to ensure consistent appraisal and transparent recommendations. The average AGREE II score for the Rigour of Development quality domain for guidelines in this review was 60/100, demonstrating considerable room for improvement across the board.

Thyroid hormone recommendations also varied despite all guidelines having the same RCT evidence base to draw on, as all RCT evidence in TRD was published prior to 2008 (Zhou et al., 2015; Strawbridge et al., 2019). Some differences may relate to variation in the point at which guidelines recommended augmentation, as (Strawbridge et al., 2019) reported just 1 RCT examining T3 in patients with 2 or more failed antidepressant treatment trials in their current episode of depression, while (Zhou et al., 2015) reported 5 studies in patients with at least 1 antidepressant treatment failure and reported it to be significantly more effective than placebo. Agreement between guidelines may therefore be limited by the absence of a universal definition for TRD (Fekadu et al., 2018). The included guidelines did employ differing criteria to indicate the use of augmentation, including differing resistance criteria (Table 3). This demonstrates the importance of the first domain of the AGREE II assessment: "Scope and Purpose," which evaluates how well a guideline specifically describes the population to whom it applies. Proper attention to this domain during development should help to make clear whether discrepancies

between recommendations are due to differences in evidence interpretation or differences in the population to which they are applicable (and therefore the relevant evidence base used). Scores on this domain had the highest mean score across included guidelines (Table 2), but there was still considerable variation, so improvements in this area can be made.

By contrast, differences between ketamine recommendations can largely be explained by differing dates of guideline publication. The MPG is both the most recently published and the only guideline to recommend (i.v.) ketamine as second line. CANMAT and the ICSI, published between 2016 and 2018, recommended ketamine as a specialist/experimental treatment. TMAP, the APA, NICE, and the CPG-S did not mention ketamine at all, but only 1 of the studies cited by the more recent guidelines predates their development (Price et al., 2009). This is with the exception of the CPG-S (2014), which broadly made recommendations in line with the NICE (2009) guidelines. Intranasal esketamine has now been approved by the US Food and Drug Administration (FDA, 2019) and European Medicines Agency (Mahase, 2019), and we can therefore expect its inclusion in future treatment guidelines. However, its role in the treatment paradigm for TRD patients remains to be established, with some healthcare payers and providers having concerns about efficacy, treatment costs, and logistics around administration. Indeed, no European Health Technology Assessment agencies have approved esketamine, unlike several US payers, and therefore differences are expected in future US vs European treatment guidelines. For example, NICE have very recently stated that they do not currently recommend its use due to uncertainties over its clinical and cost effectiveness, though their appraisal remains in progress (NICE, 2020).

This raises 2 important issues. First, the importance of regular guideline updates. Although it is not possible for any guideline to remain completely up to date, regular updates to the core guidance are clearly necessary. For example, the current full NICE guidance for MDD remains the 2009 version included in this review, though additional advice such as the decision not to recommend esketamine is made via their website. This does allow the provision of guidance in line with the latest developments in research and licensing but relies on users seeking this additional information out rather than simply being able to use their current full edition. Of course a balance has to be struck between updating the full guideline regularly and providing interim updates, but it is arguable that in the case of NICE (along with other guidelines in this review, such as the widely used APA guidelines), the interval since the last full update is too long given the subsequent advances in research and drug approval. A negative consequence of this may be the underuse of new and potentially more efficacious or tolerable treatments in clinical practice. Secondly, the decision by NICE not to recommend esketamine at present in contrast with US payers and insurers highlights the relevance of guideline affiliation and local context. NICE is the payer for the publicly funded National Health Service (NHS) in the UK, and therefore consideration of cost effectiveness plays a large role in their decision-making and their guidance is of primary utility to NHS clinicians. This may not be the case for guidelines produced by other governing bodies, and therefore recommendations may differ. This in itself is justifiable, providing that guidelines explicitly state the intended context for their use and the weighting of factors such as cost effectiveness and research evidence in their decision-making. We suggest this is not explicit enough at present.

Other Recommendations

The greatest discrepancy between guidelines was in their monitoring and discontinuation advice, particularly for lithium, in which regular monitoring is of the utmost importance to ensure patient safety. This has the potential to be not only misleading but also potentially dangerous, as guidelines commonly fail to clarify whether their recommendations are comprehensive or provide a brief summary and might account for some of the substandard monitoring reported in clinical practice. According to a recent review, only approximately 50% of lithium serum levels were within the recommended range for patients with bipolar disorder in 1 NHS trust, while adherence to safety and monitoring for recommended renal and thyroid tests was between 21% and 39% (Nikolova et al., 2018). Another review stated that only 60% of clinical trials and audits met safety monitoring standards for the prescription of lithium in the United Kingdom, and none fully met the recommendations (Aubry et al., 2017). Similarly, monitoring rates are suboptimal for AAPs (predominantly reviewed in patients with schizophrenia-spectrum disorders; Mitchell et al., 2012). The role of guidelines should be to support the highest standard of patient care, but instead our findings suggest that poor monitoring could be partially attributable to discrepancies between treatment guidelines, as unclear guidance has previously been cited as a problem leading to inconsistent care and may contribute to clinical uncertainty and subsequent treatment underutilization (Hollingshead et al., 2015). A recent consensus statement pertaining to antidepressant adverse events confirmed the need for adequate risk assessment and safety monitoring when initiating pharmacological treatment for depression (Dodd et al., 2018), and so this should be an essential part of any treatment guideline, particularly where polypharmacy is concerned. In this review, the MPG guidelines had the most detailed monitoring advice, but as it is not freely available online usability is somewhat limited.

Quality Assessment

As mentioned, some inconsistencies may be accounted for by differences in guideline quality. All eligible guidelines were assessed using the AGREE II tool (supplementary Table 1). Nine did not meet the cut-off for inclusion, scoring lowest on "rigor of development," "editorial independence," and "applicability," which relate to the likely barriers and facilitators to implementation and resource implications. The link between guideline quality and discrepant recommendations is best demonstrated by TMAP, which had the lowest mean score across quality domains and often made recommendations at odds with other guidelines. TMAP was also the only guideline to consistently fail to cite the evidence on which their recommendations were based and were the only commercially funded guideline (though the ICSI received sponsorship from private member medical groups). Adherence to a set of general guideline development rules, and the use of a consistent evidence grading system such as the recent WFSBP guidelines on how to grade treatment evidence for guideline development (Hasan et al., 2019), may improve the overall quality of treatment guidelines and support greater alignment between future recommendations irrespective of funding source or stakeholder involvement.

Limitations

Despite the comprehensive nature of this review, there are some limitations. A range of possible reasons for inconsistencies has

been discussed, including differences in evidence interpretation, but it is also possible that the licensing and availability of medications around the world may have contributed more extensively than discussed. Thus, some indication of the degree to which local drug licensing and availability have influenced the recommendations made would be valuable in future guidelines.

It is also important to acknowledge that recommendations can only be as good as the evidence on which they are based. The Strawbridge meta-analysis clearly demonstrates the paucity of RCT evidence for pharmacological augmenters in patients who have failed to respond to 2 antidepressants (Strawbridge et al., 2019), the point at which many of guidelines recommended augmentation (Table 3). There is also a need, acknowledged by some, for more head-to-head studies with a longer term follow-up, potentially improving consistency across guidelines and more comprehensive discontinuation advice. Further, patients in a clinical trial may not truly reflect the wider population, limiting the generalizability of the results and demonstrating the need for more pragmatic and naturalistic RCTs examining real-world efficacy. This would ensure that guidelines are able to accurately meet the needs of their target population.

There is also the potential issue of publication bias, as null trials may not be considered when formulating recommendations. Recent publication of null results in high-profile journals, such as antidepressant augmentation with metyrapone for TRD (McAllister-Williams et al., 2016), supports progress in this area. Finally, our review only included guidelines available in English, and therefore it is possible that some widely used publications have not been considered. Additionally, recommendations relevant to specific subpopulations or specialist groups (e.g., pregnant women or older patients) and adjunctive agents that were not listed as first or second-line by at least 1 of the included guidelines were not reviewed, which would be of benefit.

Future Directions

It is clear from the findings of this review that changes are needed to the way in which treatment guidelines are developed to ensure that they support clinicians and facilitate the provision of high-quality evidence-based care. The number of available guidelines and the apparent variation in their quality is cause for concern. The collective requirement by publishing bodies for the application of a guideline development tool, equivalent to the Vancouver Recommendations provided by the International Committee of Medical Journal Editors (ICMJE, 2019) or the widely used Consolidated Standards of Reporting Trials statement for RCTs (Schulz et al., 2010), would be of great benefit. The quality domains outlined in the AGREE II recommendations (Brouwers et al., 2010) provide a strong basis for this, but consistent application to psychiatric guidelines has not been achieved and additional consideration of need is warranted. This review includes guidelines from around the world that have the potential to be beneficial given global differences in treatment cost, availability, and acceptability. However, such considerations were not clearly reflected in the recommendations, and therefore the need for such a range of publications from several sources is questionable. The expectation for developers to use a tool such as the AGREE II and explicitly state the unfulfilled need their publication meets would ensure that published guidelines are both necessary and of good quality.

Conclusions

To our knowledge, this is by far the most comprehensive review of augmentation treatment guidelines for unipolar depression. Although some differences are inevitable given the limited evidence base and the somewhat subjective nature of balancing factors such as efficacy and tolerability, greater consistency could be achieved by the standardization of development. This review will therefore aid future guideline development in this field and beyond as well as serve as a useful tool to comprehensively summarize the treatment recommendations for clinicians and researchers working in unipolar resistant depression.

Supplementary Materials

Supplementary data are available at *International Journal of Neuropsychopharmacology (IJNPPY)* online.

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Statement of Interest

In the last 3 years, A.J.C. has received honoraria for speaking from Lundbeck; honoraria for consulting from Allergan, Livanova, Janssen, and Lundbeck; and sponsorship for attending an academic conference from Janssen. A.H.Y. has received honoraria for speaking from Astra Zeneca, Lundbeck, Eli Lilly, Sunovion; honoraria for consulting from Allergan, Livanova and Lundbeck, Sunovion, Janssen; and research grant support from Janssen in the last 3 years. R.Z. provides private psychiatric services at The London Depression Institute; is an honorary PI at D'OR Institute for Research & Education, Rio de Janeiro, a not-for-profit organization; on the Advisory Board for Science, a US not-for-profit organization; has consulted for Fortress Biotech; is a co-investigator on a Livanova-funded study; has received speaker honoraria for medical symposia and educational activities from Lundbeck and Janssen; and collaborates with Janssen, EMIS PLC, and Alloc Modulo Ltd. L.M. is an employee of COMPASS Pathways Ltd. No other authors have conflicts of interest to declare. It is also worth noting that A.J.C. is the lead author of the British Association of Psychopharmacology (BAP) guidelines included in this review and A.H.Y. is an author of the included Maudsley Prescribing Guidelines (MPG), on which A.J.C. is acknowledged for his contributions. Neither A.H.Y. nor A.J.C. received financial benefits for their involvement in writing these guidelines. A.H.Y. and A.J.C. were not involved in the quality review of the guidelines in this manuscript: this was conducted by authors R.T., L.M., E.O., V.D.A., S.M., and B.V.

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