Protocol for a systematic review of the pharmacological augmentation treatment guidelines for unipolar depression

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Key words

Depression, Augmentation, Guideline, Pharmacology

Contributions

The study protocol was drafted by RT and LM, with support in the development of methodology, search strategy and inclusion criteria provided by AJC. All other co-authors were involved in the conception and design of the study.

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Conflicts of Interest

AC has in the last three years received honoraria for speaking from Astra Zeneca (AZ) and Lundbeck, honoraria for consulting from Allergan and Livanova and research grant support from Lundbeck. AMP is supported by Bionomics Limited. No other review team members report any conflicts of interest.

Background and Rationale

There are a range of available treatments for major depressive disorder, including pharmacological, psychological and neurostimulatory options. To select an appropriate therapy, clinicians may refer to the advice offered by current treatment guidelines, which are published independently by local, national and international bodies. However, treatment guidelines for depression are not standardised, and a universal or 'first line' guideline does not exist. It is therefore plausible, given the number of treatments available, that recommendations may differ between them as may the evidence on which the guidelines are based, and their overall quality.

An overview of the quality and content of recommendations made by available guidelines could benefit both clinicians and their patients. Response rates to both pharmacological and psychological treatment in patients with major depressive disorder (MDD) vary widely, with as many as 30-50% of patients having an inadequate response to at least two different antidepressant treatments (Cleare et al., 2015). If discrepancies exist between the quality and content of treatment guidelines, it is important that clinicians are aware, and therefore able to give consideration to this when making treatment decisions.

MDD patients who do not respond to initial antidepressant treatment(s) may be regarded as treatment resistant, and this has been associated with poorer long term outcomes (Fekadu et al., 2009). Therefore, the assessment of treatment guidelines for this group is of particular importance, to ensure clinicians are able to make the best possible treatment decisions based on the available evidence and guidance. Pharmacological augmentation, whereby another agent is added to an existing antidepressant treatment, is a widely used strategy for this patient group. As there are a large number of pharmacological augmentation options available, guidelines for this line of treatment will be the focus of this review. In doing so we hope to provide a concise overview for both clinicians and researchers.

Objectives

Objectives: To provide a comprehensive overview of recommendations made by local, national and international bodies for the prescription of pharmacological augmentation therapies for TRD, to identify consistencies and inconsistencies between them, and to assess their quality. It is therefore hoped that this review may identify barriers to the prescription of pharmacological augmentation therapies and highlight areas for future research.

Methods

Eligibility criteria

Records identified by the search will be assessed for eligibility in 2 stages:

Stage 1 guideline selection:

All current versions of local, national and international guidelines meeting the following eligibility criteria will be included at this stage:

- Guidelines for treating clinicians. For the purpose of this review we will use the following definition of a guideline: *Statements that include recommendations intended to optimise patient care that are informed by a review of evidence and an assessment of the benefits and harms of alternative care options*. This

definition is adapted from that used by (Verdolini et al., 2018), and based on those stated by the Institute of Medicine (Institute of Medicine (U.S.) & Graham, 2011).

- Published in the past 10 years
- Available in English
- The guidelines must relate to the management of adults (18+ years) with unipolar MDD. Recommendations for specific subsets of MDD patients, e.g. those who are pregnant or breastfeeding, will not be included.
- The guidelines must mention pharmacological augmentation as a treatment option in order to be included.

Stage 2 guideline selection:

All guidelines meeting stage 1 eligibility will be assessed for quality using the Appraisal of Guidelines for Research and Evaluation (AGREE) II tool (Brouwers et al., 2010) as per the methodology outlined below. Those with a total score of >=100 for domains 1 to 6 will be included in this stage and assessed for content.

Information sources and search strategy

A systematic search of the MEDLINE, PsychINFO and Embase databases will be conducted, using terms relating to guidelines, augmentation treatment, and treatment resistant depression (see search terms of article title and abstracts below). To ensure all relevant literature is included, we will review the reference list of all included articles and any relevant reviews for additional guidelines.

Search terms: ("guid*" OR "consensus" OR "recommend*" OR "algorithm*" OR "expert panel" OR "advi*") AND ("depress" OR "MDD") AND ("treat*" OR "therap*").

Study records and selection process

All study records identified by the search will be downloaded to EndNote (https://endnote.com/) and duplicates removed. 2 review authors (RT and LM) will independently screen titles and abstracts for each record. For those appearing to meet the stage 1 inclusion criteria or where there is any doubt, review authors will assess the full text for eligibility. Any discrepancies between the review authors regarding suitable records will be discussed until a consensus is reached. A third review author (AJC) will be consulted as necessary.

All records meeting stage 1 eligibility will then be assessed for quality by 2 review authors (RT and LM) using the AGREE II tool. All those meeting a total score of >=100 for domains 1 to 6 will go to data extraction.

Data extraction

Relevant data will be extracted for all included guidelines meeting stage 2 eligibility criteria. This will be done for all pharmacological augmentation treatments recommended by at least one of the included guidelines. Data pertaining to recommendations for treatments that are lower than second line in all guidelines will not be retrieved. Data extraction will be completed independently by 2 authors for each guideline (RT, LM, EO, VA, SM and BV) and any discrepancies reviewed.

Outcomes and prioritisation

Primary outcomes:

1. Recommended augmentation treatments, including indication/contraindication, pre-prescribing and monitoring tests, dosage, and tapering/withdrawal recommendations.

Secondary outcomes:

1. Discrepancies between guidelines in recommendations
2. Quality of guidelines identified by the search as assessed by the AGREE II tool.

Data Synthesis

Data about the quality of guidelines will be evaluated qualitatively. For studies reaching stage 2 inclusion, relevant treatment data will be extracted from the guidelines, and recommendations for indication/contraindication, pre-prescribing and monitoring tests, dosage, and tapering/withdrawal will be summarised, along with the literature on which they are based. Similarities and inconsistencies between guidelines will be reported.

Dissemination Plans

It is intended that the results of the study will be published in open access, peer-reviewed journals. In addition, we will present the findings at National and International conferences to reach as wide an audience as possible.

References

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