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Antipsychotic augmentation for major depressive disorder: A review of clinical practice guidelines

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ABSTRACT

Clinical Practice Guidelines (CPGs) are seen as the gold standard of evidence-based care. Because of their influence, these guidelines can have profound legal and economic effects. Despite their proliferation and influence, the trustworthiness and quality of guidelines have been seriously questioned and they have been implicated as drivers of overtreatment. In the U.S, augmentation with second generation antipsychotics (SGAs) is becoming an increasingly common strategy for treating major depressive disorder (MDD) when initial antidepressant treatment does not result in remission of symptoms. However, there is debate about the evidence for augmentation and whether this strategy is a form of overtreatment. We conducted a systematic search to identify treatment guidelines for MDD. Fourteen international guidelines met inclusion criteria and we reviewed them to determine: 1) if augmentation with SGAs was recommended for patients who did not respond to antidepressant medication; 2) what evidence was cited for the recommendation for or against augmentation; 3) the extent to which the guidelines addressed risk/benefit concerns when making their recommendations. There was significant variation among the CPGs regarding the recommendation to augment with antipsychotic medication for Major Depressive Disorder. Seven guidelines explicitly recommended augmentation with antipsychotics; 1 guideline reviewed the evidence but neither recommended for nor against; 1 guideline did not make a clear recommendation; 2 guidelines explicitly recommended against augmentation; and 3 guidelines did not address augmentation with antipsychotics as a potential treatment strategy. There was wide variation in terms of attention to risk/benefit issues and to the conditions under which augmentation should be considered. The results are discussed in terms of the implications for risk management and informed consent practices.

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1. Introduction

Clinical practice guidelines (CPGs) were developed to enhance the practice of evidence-based medicine and, by extension, collaborative decision-making and the practice of informed consent. Guidelines play a major role in malpractice suits and decisions about what will (and will not) be covered by insurance companies and government programs, and they have profound consequences for patient care. However, despite their proliferation and influence, the trustworthiness and quality of guidelines have been seriously questioned (Kung, Miller, & Mackowiak, 2012; Shaneyfelt, 2012) and they have been implicated as drivers of overtreatment. Guidelines sometimes serve to codify common medical practices that are not evidence-based, therefore driving medical overuse (Fava, 2014; Morgan, Dhruva, Wright, & Korenstein, 2015). Major depressive disorder (MDD) is one such area of risk because of the frequency of residual symptoms in those who initiate medical treatment. Less than half of patients prescribed antidepressants in outpatient settings respond to medication, and less than one-third experience remission (Trivedi et al., 2006). As a result, clinicians may turn to CPGs to provide them with strategies for what has been termed "treatment resistant depression" (TRD).

Monotherapy with antidepressants is often recommended as a first-line intervention for all levels of depression, although it should be noted that extensive evidence exists for therapeutic interventions (e.g. cognitive-behavioral therapy, interpersonal therapy; Cosgrove et al., 2017). In the U.S., augmentation with a second-generation antipsychotic medication (SGA) is becoming an increasingly common strategy when initial antidepressant treatment does not result in remission of symptoms. However, there is debate over the evidence for augmentation, whether this strategy is a form of overtreatment, and strong concerns about tolerability and side effects, including agranulocytosis, stroke, cardiovascular disease, sedation, elevated prolactin levels, metabolic syndrome and weight gain (Moore & Furberg, 2016; Shelton, 2015; Üçok & Gaebel, 2008).

Given the range of alternative strategies for TRD—from cognitive behavioral therapy and behavioral activation to electroconvulsive shock therapy and transcranial magnetic stimulation—and the well-documented side effects associated with SGAs, physicians need guidance when considering treatment options. From both a risk management and informed consent perspective, harms and benefits must be carefully assessed when considering these options. Our aims were to 1) evaluate treatment guidelines for MDD to determine whether augmentation with an SGA was recommended; 2) identify the meta-analyses that were cited as evidence; and 3) assess the extent to which the guidelines addressed risk/benefit concerns when making their recommendations.

2. Method

We searched MEDLINE, the Trip search engine, and the International Guideline Library of the Guidelines International Network to identify guidelines (see Appendix A for search terms and strategy). We adopted the Institute of Medicine's (IOM) definition of a guideline: "Clinical practice guidelines are statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options" (IOM, 2011). We restricted the search to guidelines originally published in English or with an English translation, with no country restriction, for the time period between 2009 and 2014. The search was then updated in March 2016 to include any new or revised guidelines. We abstracted the recommendations from identified CPGs regarding augmentation with SGAs, and evaluated the evidence cited in support of these recommendations and the degree to which individual guidelines addressed risk/benefit concerns when making their recommendations.

We used a predefined template which included the following domains: 1) recommendation regarding adjunctive use of antipsychotic medication (Yes, No, Unclear/Review but no recommendation, Not addressed); 2) recommendation, where applicable, regarding the timing of augmentation; 3) the strength of the evidence used to support augmentation; and 4) the evidence cited in the CPG as evidence for or against augmentation. We excluded recommendations concerning augmentation for MDD with psychotic features. Recommendations were extracted by one of the co-authors (PS) and reviewed for accuracy by a practicing psychiatrist (HB).

Although complex and heterogeneous RCT data pose challenges (Lorenc et al., 2016), meta-analysis is considered to be one of the strongest forms of evidence to support clinical practice and it is used in systematic reviews to obtain summary estimates of treatment effects (Cosgrove, Vannoy, Mintzes, & Shaughnessy, 2016). The meta-analyses cited by the CPGs were also entered into the template.

3. Results

Our search identified 14 guidelines for the treatment of MDD. In terms of the first aim, we found significant variation regarding the recommendation to augment with SGAs (hereafter referred to as "augmentation") for MDD (see Fig. 1). Seven guidelines recommended augmentation; two guidelines explicitly recommended against augmentation; one guideline reviewed the evidence but stated "The GDT makes no recommendation for or against" (Kaiser Permanente, 2012, p. 5), citing "lack of longer-term data, known cardiometabolic risks […] and lack of comparison data" (p. 5); and three guidelines did not mention augmentation at all. One guideline (UMHS, 2011) had wording that did not fit into any of these categories:

> Some primary care physicians will feel comfortable using pharmacologic augmentation strategies with their patients who do not respond to standard antidepressant regimens. Primary care physicians might consider the following strategies, which are commonly used by experts in depression care […] Many of the above augmentation strategies have limited evidence of efficacy and studies supporting their effectiveness often have methodological limitations. The exceptions to this are ECT, MAOIs and lithium supplementation, and perhaps antipsychotic augmentation, although, to date, most studies examining the effectiveness of the latter strategy have been drug company supported. (p. 13–14).

The use of existing meta-analyses evaluating augmentation with an SGA (aim 2) is outlined in Table 4. Only six (43%) of the CPGs supported their recommendations with one or more meta-analyses, and the guideline development groups reached different conclusions about augmentation with APs (see Table 5). Three meta-analyses concluded in favor of augmentation, while two did not make any explicit recommendation, emphasizing poor tolerability and the potential for treatment related harm. Although the Cochrane group is considered the gold-standard when it comes to research integrity, particularly for meta-analysis (Ioannidis, 2016), only one guideline cited its 2010 meta-analysis despite the fact that nine CPGs (64%) were published after that date. Of the seven guidelines that recommended augmentation, only four cited meta-analyses; these four cited only meta-analyses that drew favorable conclusions. Of the two guidelines that recommended against augmentation, one cited only meta-analyses that were conservative in their recommendations (including the Cochrane review), while one cited both a meta-analysis that was conservative as well as one that was in favor of augmentation. It is also noteworthy that none of the guidelines recommending augmentation addressed the issue of tapering or timeline to discontinuation of antipsychotic medication.

Indicators of the quality of the evidence as well as the strength of the recommendation varied among CPGs (see Table 1). Three of the guidelines recommending augmentation provided clear ratings, but the remaining four guidelines did not. NCCMH (2010) rated the individual studies they considered, but did not rate the overall evidence. avalia-t (Working Group of the Clinical Practice Guideline on the Management of Depression in Adults, 2014) rated the evidence variously as Levels B and C, depending on which section one reads. Map of Medicine (2012a, 2012b, 2012c, 2012d) and ICSI (Mitchell et al., 2013) did not provide a