Invited Commentary

Medicating Distress

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Chlorpromazine hydrochloride first became available in Europe and the United States in the early 1950s. A large, double-blind, placebo-controlled trial that was conducted within the US Veterans Affairs system and included nearly 700 patients (all men aged ≤50 years) helped establish its efficacy for treating schizophrenia.[1] The use of chlorpromazine is credited with large decreases in psychiatric inpatient populations around the world, as well as prompting a widespread search for other antipsychotic drugs.

However, before the study on schizophrenia was published in 1960,[1] advertisements marketing chlorpromazine (as Thorazine) appeared in the late 1950s for a host of indications and populations, ranging from "prompt control of senile agitation" (featuring a white-haired older man wielding an upraised cane) to "prompt control of nausea and vomiting in children" (with a child leaning over a sink) to "relief from the suffering and mental anguish of cancer." But why stop there? Advertisements also touted Thorazine for the treatment of arthritis, acute alcoholism, and the "psychic stress" of severe asthma. For all varieties of distress, apparently chlorpromazine and similar antipsychotic drugs were the solution.

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By 1990, more than 40 antipsychotic drugs had been marketed worldwide,[2] although the indications for use had been narrowed since the 1950s. Although severe asthma is not a common reason for use of antipsychotic drugs in 2016, they are still used for perceived benefit in reducing "psychic stress" or distress. As such, antipsychotic drugs have a long history of use for treating delirium associated with severe or terminal medical illness, although rigorous evidence supporting this use is sparse.[3] In this issue of *JAMA Internal Medicine*, Agar and colleagues[4] provide critical evidence to help guide the use of antipsychotic drugs for delirium in patients receiving palliative care. The short answer is: don't.

The study targeted symptoms of delirium that are associated with distress: inappropriate behavior, inappropriate communication, and illusions or hallucinations. Haloperidol and risperidone were not only not better than placebo but these symptoms actually worsened in patients randomized to receive the antipsychotic drugs, while the patients' overall delirium also worsened. As would be expected, patients receiving the antipsychotic drugs experienced more extrapyramidal effects. Perhaps most concerning, median time to survival was shorter for patients taking antipsychotic drugs, and these patients were approximately 1.5 times more likely to die. This finding is remarkable in a placebo-controlled trial in which patients received just 6 doses of study medication (or placebo) in 72 hours. Hopefully, the study by Agar et al[4] will help convince health care professionals that, in using antipsychotic drugs to treat delirium in terminally ill patients, not only are they not reducing distress but they are in fact worsening patients' symptoms.

What happens now with the use of antipsychotic drugs in this patient population? It may be useful to consider the use of antipsychotic drugs in patients with dementia as a potential guide. The advertisement for Thorazine with the white-haired gentleman wielding a cane illustrates that, since their development, antipsychotic drugs have been seen as useful to treat the distressing behavioral and psychological symptoms of dementia (BPSD). However, as manufacturers sought approval to use the newer atypical antipsychotic drugs specifically for distressing BPSD, it became clear that their use caused an increased risk of death relative to placebo.[5] In 2005, the US Food and Drug Administration issued a black box warning regarding the increased risk of mortality associated with the use of atypical antipsychotic drugs to treat BPSD.

Although the use of atypical antipsychotic drugs did decrease after this warning was issued, the use of conventional antipsychotic drugs, which had been declining up to that point, plateaued. In addition, the use of other psychotropic drugs that were not antipsychotics, with even less evidence of benefit but lacking definitive evidence of harms, grew.[6] And today, despite more than a decade of evidence about the harms of using antipsychotic drugs to treat distressing BPSD, their use persists, along with the use of other psychotropic drugs with minimal evidence of benefit. Although nonpharmacologic (better termed *ecobiopsychosocial*) management of BPSD is promoted as first-line treatment instead of medication by nearly every expert group, such strategies lack an industry behind them to promote and profit from their implementation in real-world practice.

Ideally, the study by Agar et al[4] will be immediately translated into practice, with a marked drop in the use of antipsychotic drugs for delirium in patients receiving palliative care. As the authors note, there are other means of reducing distress in these patients, beginning with identifying delirium, reversing precipitants of delirium, and providing supportive interventions.[7] But the experience with the use of antipsychotic drugs in dementia, where there are many evidence-based, ecobiopsychosocial interventions for patients and caregivers, suggests that this change in practice is unlikely.[8] Such alternatives can be time-consuming and are not incentivized in the current reimbursement systems in the United States. As a result, for physicians and other prescribing clinicians, all too often the desire to reduce patient distress is reduced to writing a prescription for a sedating psychotropic medication.

How will this practice change for patients with delirium, dementia, or both? First, clinicians must recognize the real potential harms to which they expose their patients by prescribing antipsychotics. And not only harms from medication-associated adverse effects or events but, for patients with delirium who are receiving palliative care, actually worsening the patient distress for which the antipsychotic is being prescribed. Second, health care professionals should recognize

when the caregiver's distress about a patient's symptom is a motivating factor in the decision to prescribe an antipsychotic medication and address that directly. A clinician also must be aware when prescribing an antipsychotic is partially motivated by his or her own distress when confronted with an ill patient. Clinicians may understandably want to reduce distress in patients with delirium who are receiving palliative care, and in some settings, certain health care professionals may believe that there are no treatment options available other than a prescription. But even where clinicians do have access to ecobiopsychosocial treatment resources, a medication may still be the most appealing intervention: as physicians, our training may leave us wanting to treat distressing symptoms through what we perceive as the most "science-based" approach (eg, the dopamine receptor blockade of antipsychotics) rather than the "softer" work of counseling and educating a distraught caregiver or implementing an environmental modification.

Choosing to not prescribe an antipsychotic should not mean not providing support and treatment. Physicians need training and resources so that they are equipped to provide environmental or biopsychosocial interventions in place of a prescription. But to fully engage in such training and shift the treatment paradigm, physicians need to let go of the idea that dopamine receptor blockade is the answer to treating distress in these patients. Some distress cannot be medicated away.

ARTICLE INFORMATION

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REFERENCES

1. Casey JF, Bennett IF, Lindley CJ, Hollister LE, Gordon MH, Springer NN. Drug therapy in schizophrenia: a controlled study of the relative effectiveness of chlorpromazine, promazine, phenobarbital, and placebo. *AMA Arch Gen Psychiatry*. 1960;2:210-220.

2. Shen WW. A history of antipsychotic drug development. *Compr Psychiatry*. 1999;40(6):407-414.

3. Devlin JW, Smithburger P, Kane JM, Fraser GL, Skrobik Y. Intended and unintended consequences of constraining clinician prescribing: the case of antipsychotics. *Crit Care Med*. 2016;44(10):1805-1807.

4. Agar MR, Lawlor PG, Quinn S, et al. Efficacy of oral risperidone, haloperidol, or placebo for symptoms of delirium among patients in palliative care: a randomized clinical trial [published online December 5, 2016]. *JAMA Intern Med*. doi:10.1001/jamainternmed.2016.7491

5. Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. *JAMA*. 2005;294(15):1934-1943.

6. Kales HC, Zivin K, Kim HM, et al. Trends in antipsychotic use in dementia 1999-2007 [published correction appears in *Arch Gen Psychiatry*. 2011;68(5):466]. *Arch Gen Psychiatry*. 2011;68(2):190-197.

7. Hshieh TT, Yue J, Oh E, et al. Effectiveness of multicomponent nonpharmacological delirium interventions: a meta-analysis. *JAMA Intern Med*. 2015;175(4):512-520.

8. Kales HC, Gitlin LN, Lyketsos CG. Assessment and management of behavioral and psychological symptoms of dementia. *BMJ*. 2015;350:h369.