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Review Article

Antipsychotic Drug Therapies: Matching primary care practice to clinical challenges

Summary

Primary health care providers prescribe over 50 percent of drug therapies for patients with mental health issues in the United States. Nonetheless, primary health care providers tend to be reluctant to prescribe antipsychotic drug therapies despite their widespread availability and favorable benefit-to-risk ratio. This may be due, at least in part, to appropriate concerns about the serious adverse effects of all earlier first generation, or typical, as well as many of the earlier second generation, or atypical, antipsychotic drug therapies.

In patients with severe mental illness, the totality of evidence supports the wider prescription of newer second and third generation atypical antipsychotic drug therapies. These drugs tend to have greater clinical efficacy as well as fewer adverse effects, especially on weight and associated metabolic consequences. The more widespread and appropriate prescription of these drugs by primary health care providers would likely improve the quality of life as well as the markedly reduced lifespan of patients with severe mental illness.

At present, the evidence from randomized trials is insufficient to draw firm conclusions about benefits and risks in nonpsychotic anxiety and behavioral symptoms of dementia.

Thus, primary health care providers should make individual clinical judgments based on the available evidence for each of their patients.

Primary health care providers are the backbone of the healthcare delivery system in the United States (US). As part of their overall focus on a person's health and wellness, they are playing an increasingly important role in identifying as well as treating mental disorders [1]. Primary health care providers prescribe over 50 percent of drug therapies for patients with mental health issues in the US. In addition, about 25 percent of all primary health care patients have diagnosable mental disorders [2]. Both these percentages are likely to increase in the US as there is also an increasing shortage of psychiatrists [3].

Many, if not, most primary health care providers are reluctant to prescribe antipsychotic drug therapies despite their widespread availability and favorable benefit-to-risk ratio. This may be due, at least in part, to appropriate concerns about the serious adverse effects of all earlier first generation, or typical, as well as many earlier second generation, or atypical, antipsychotic drug therapies [4], This Special Report provides recent evidence for primary health care providers which has the potential to change practice patterns by increasing their prescription of antipsychotic drug therapies to those with severe mental illness as well as, perhaps to a wider range of their patients with other disorders such as nonpsychotic anxiety and behavioral symptoms of dementia.

Antipsychotic drug therapies are approved by the US Food and Drug Administration (FDA) to treat acute psychoses, as well as to manage several manifestations of severe mental illness, including schizophrenia and bipolar disorder. They are also used as adjunctive drug therapies with antidepressants in major depressive disorders. Antipsychotic drug therapies were initially divided into two classes, first and second-generation [5,6]. The first generation, or typical, antipsychotic drug therapies, are far older, having been first approved by the US FDA in the late 1950s. The earlier second generation,

or atypical antipsychotic drug therapies, namely risperidone and quetiapine, were approved by FDA in 1994 and 1997, respectively. The most recent second generation drug to be approved by FDA was cariprazine in 2015 (Table 1).

Table 1: First, Second and Third Generation Antipsychotic Drug Therapies with Dates of FDA Approval of Second Generation Drugs.

First Generation	Second Generation	Third Generation
chlorpromazine (Thorazine)	asenapine (Saphris) 2009	aripiprazole (Abilify)
fluphenazine (Prolixin)	cariprazine (Vraylar) 2015	brexpiprazole (Rexulti)
haloperidol (Haldol)	clozapine (Clozaril) 2002	
loxapine(Loxitane)	iloperidone (Fanapt) 2009	
molindone(Moban)	lurasidone (Latuda) 2010	
perphenazine(Trilafon)	olanzapine (Zyprexa) 2009	
pimozide (Orap)	paliperidone (Invega) 2006	
thioridazine (Mellaril)	quetiapine (Seroquel) 1997	
thiothixene (Navane)	risperidone (Risperdal) 1994	

Second generation atypical antipsychotic drug therapies have better tolerability as well as safety profiles. Perhaps of even greater importance to primary healthcare providers and their patients, with respect to safety, the second when compared with the first generation antipsychotics, produce significantly fewer extrapyramidal symptoms, most notably, the serious and often irreversible symptom of tardive dyskinesia [5,6]. These major improvements have made second generation antipsychotic drug therapies a preferred choice for psychiatrists as well as primary health care providers and their patients. Nonetheless, many of the earlier drugs in this class produced major amounts of weight gain as well as other adverse metabolic consequences that have posed clinical challenges to primary healthcare providers as well as their patients. These severe adverse metabolic effects include major amounts of weight gain, dyslipidemia, hypertension, and insulin resistance leading to diabetes mellitus, all of which constitute metabolic syndrome. Metabolic syndrome has been termed the "new silent killer" because the average primary prevention subject in the US with this condition has a 10 year risk of a first coronary event of about 16-18%. This level of risk for a primary prevention subject is almost as high as the risk of a recurrent event in a secondary prevention patient [7]. Further, this serious condition is also extremely common in the general population of adults in the US. Specifically, metabolic syndrome affects 40% over age 40 years and a far greater proportion of patients with severe mental illness. Further, patients with severe mental illness, when compared to the general population, tend to have about a two-fold increased prevalence of metabolic syndrome Thus, the prescription of atypical antipsychotic drug therapies with adverse metabolic consequences has led to alarming increases in the prevalence and severity of metabolic syndrome in patients with severe mental illness [4].

Patients with severe mental illness also have a higher prevalence of other risk factors which contribute to their development of premature cardiovascular disease events and death. For example, up to 75%, of patients with severe mental

illness are cigarette smokers compared with about 15% of the general population [8]. Further, patients with severe mental illness when compared to the general population, whether in primary or secondary prevention of coronary heart disease, are significantly less likely to be prescribed drug therapies of proven benefit, including aspirin, statins, beta-blockers and angiotensin converting enzyme inhibitors or blockers. Finally, even when prescribed these drugs such patients have lower adherence. Thus, there is less access to as well as utilization of medical care of life saving benefits. As a consequence of all these factors, such patients have a markedly reduced lifespan, on average 15 to 25 years less than the general population [9]. Coronary heart disease is, far and away, their leading cause of premature death despite the fact that patients with severe mental illness have a tenfold higher lifetime risk of suicide of 10% compared with the general population rate of about 1%. All these considerations support the need for primary health care providers to prescribe atypical antipsychotic drug therapies that do not further exacerbate the already high prevalence of the adverse metabolic risk factor profile of either primary prevention subjects or secondary prevention patients, both of whom are at markedly increased risks for premature cardiovascular disease events and death [8,9].

Fortunately, a recent refinement of second generation antipsychotics with differing neurotransmitter profiles has led to the introduction of the term third generation antipsychotics to describe aripiprazole in 2002 and brexpiprazole in 2015 (Table 1). While aripripazole has been far more widely studied, both these third generation antipsychotic drug therapies have comparable efficacy to second generation atypical antipsychotic drugs and produce far fewer adverse metabolic consequences than earlier agents in the class [5,6].

The Clinical Antipsychotic Trials of Intervention Effectiveness [10], tested some, but not all, of the earlier second generation antipsychotic drugs, including olanzapine, quetiapine, risperidone and ziprasidone. One primary outcome was weight gain over an 18-month period in patients with chronic schizophrenia treated for an average of more than 14 years. Olanzapine, quetiapine and risperidone all produced significant weight gain. In fact, olanzapine produced the most weight gain of about 36 pounds, compared to quetiapine, which produced weight gain of about 9 pounds and risperidone, which produced weight gain of about 7 pounds. In contrast, patients assigned at random to ziprasidone, lost about 5 pounds. Thus, the majority of these earlier second generation antipsychotic drug therapies produced severe metabolic consequences which further increased the already adverse cardiovascular risk profile of patients with severe mental illness. For example, the most frequently prescribed antipsychotic drug in the United States and many other countries has been quetiapine [11], which produces adverse metabolic effects [10]. In contrast, it is also notable that for bipolar I depression alone or as adjunctive therapy, lurasidone, a newer second generation antipsychotic drug with minimal metabolic effects, has been approved for bipolar and mixed depressive disorders, in addition to its prior indication for the treatment of chronic schizophrenia [6].

Recently, randomized evidence has been published for what has been termed the third generation atypical antipsychotic drugs, especially aripiprazole, with comparable efficacy and more favorable weight and metabolic side effect profiles [5,6] (Table 1). In addition, aripiprazole is recommended for the treatment of schizophrenia as well as for the acute treatment of manic and mixed episodes of bipolar I disorder, and for agitation associated with either of these disorders. Further, patients with chronic schizophrenia can be successfully switched from an older second generation antipsychotic drug with metabolic consequences such as olanzapine or quetiapine to a newer second generation drug such as lurasidone or third generation drug such as aripiprazole, without detrimental effects. In one randomized trial, patients with schizophrenia and metabolic syndrome were assigned to aripiprazole or continued on olanzapine. Those allocated at random to aripiprazole experienced significant decreases in body weight, dyslipidemia, hypertension, and insulin resistance leading to diabetes. Thus, a large proportion of patients who were switched at random from olanzapine to aripiprazole had decreases in the severity or even continued occurrence of their metabolic syndrome [12].

In addition to their recommended use in severe mental illness, the availability of newer second generation and third generation antipsychotic drugs with fewer metabolic consequences, has raised consideration of their possible favorable benefit-to-risk ratio for other non-psychotic but persistent, disabling and refractory conditions, including anxiety [13], and behavioral symptoms of dementia [14], For example, aripiprazole has been shown to have efficacy in refractory generalized anxiety and could potentially play a role in the treatment of various anxiety disorders, either alone or as adjunctive therapy with antidepressants [13]. It should also be noted that one major concern for the treatment of the behavioral symptoms in elderly patients with dementia with second generation antipsychotic drug therapies derived initially from adverse event reports to the US FDA [15]. This led to the formulation of the hypothesis that atypical antipsychotics increase the risks of stroke and mortality in elderly patients with dementia and resulted in a black box warning. In this regard, it is important to note that adverse event reports have no comparison group so they are useful to formulate but not to test hypotheses. Thus, the alternative hypothesis of no association was also plausible due to uncontrolled and uncontrollable confounding due to severity of illness and preexisting health conditions, which has been termed confounding by indication [16]. The most reliable design strategy to test the most plausible small to moderate effects is a large scale randomized trial [17]. In this regard, the Clinical Antipsychotic Trials of Intervention Effectiveness tested the hypothesis in elderly patients with Alzheimer's disease and dementia. Patients assigned at random to olanzapine, quetiapine, and risperidone. all of which produce serious adverse effects on weight and associated metabolic consequences, had increased risks of mortality [18], With respect to aripiprazole, however, which is less likely to produce weight gain and associated metabolic consequences, randomized data suggested net benefits [19].

In patients with severe mental illness, the totality of available evidence supports the wider prescription of newer second or third generation atypical antipsychotic drug therapies. These drugs have clinical efficacy as well as fewer adverse effects on weight and associated metabolic consequences. The more widespread prescription of these drugs by primary health care providers would likely improve the quality of life by reducing symptoms as well as improve the markedly reduced lifespan, some of which is attributed to metabolic syndrome, of patients with severe mental illness.

In choosing the most appropriate antipsychotic drug therapy, primary healthcare providers should consider the most current evidence in the context of the characteristics of their individual patients. Further research is certainly needed to investigate the possibilities for the expanded utilization of second and third generation agents. At present, however, the available evidence from randomized trials is insufficient to draw firm conclusions about benefits and risks in nonpsychotic anxiety and behavioral symptoms of dementia. Thus, primary health care providers should make individual clinical judgments based on the totality of evidence for each of their patients.

Conflicts of Interest

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