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Recommendations for the Monitoring of Serum Concentrations of Antipsychotic Drugs in the Treatment of Schizophrenia

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A 40-year-old man with schizophrenia is being treated with the long-acting injectable form of risperidone. He comes to a community clinic for his second 50-mg dose since beginning treatment. His psychiatrist instructs him to stop concomitant use of oral risperidone 1 week after the second injection, as is recommended by the drug manufacturer. Three days following discontinuation of oral risperidone, the patient becomes fearful that his son, who lives with his ex-wife, has been kidnapped. He reaches this conclusion based on FBI and CIA radio transmissions that he believes he can hear being emitted from parked cars. He attempts to contact his family with this information and ultimately calls the police to his ex-wife's home. When his family gets word of his decompensation, they bring him to the closest emergency room and he is admitted to an inpatient psychiatric facility. On admission, his combined serum level of risperidone and 9-OH-risperidone is found to be 10.4 ng/mL, approximately half the lower limit of the therapeutic range recommended by AGNP guidelines. Could evaluation of his serum level of risperidone prior to discontinuation of the oral medication have prevented this relapse and rehospitalization?

Antipsychotic drugs, drugs that work primarily through antagonism at the D_2 subtype of the dopamine receptor, have been the mainstay of the treatment of schizophrenia and related illnesses since the introduction of chlorpromazine in 1954. Over the last 60 years, more than 50 compounds have been introduced into clinical practice, each with its own set of dosing recommendations, drug-drug interactions, and adverse effects. Despite the level of challenge and complexity intrinsic to the management of such a varied set of compounds, however, most psychiatrists continue to monitor the efficacy and safety of antipsychotics in patients with schizophrenia through clinical observation and patient self-report, without the aid of more objective measures. Additionally, although the establishment of medication adherence remains perhaps the most important factor in the prevention of relapse for patients with schizophrenia, physicians routinely rely on information elicited through interview for this purpose rather than on direct investigation through laboratory measures.

For the aforementioned reasons, therapeutic drug monitoring (TDM), the measurement of drug levels directly affecting clinical decision making, has the potential to add great value in the management of patients with schizophrenia. Although TDM is routine practice in some areas of psychiatry, particularly in the management of mood stabilizers and tricyclic antidepressants, its adoption into the management of antipsychotic drugs has been slow. This state of affairs persists despite a fairly large body of literature supporting the use of TDM with antipsychotics and, as of 2011, the establishment of consensus guidelines regarding monitoring parameters.[1] The aim of the present article is to communicate the existing data and current expert consensus on the monitoring of antipsychotic drugs in patients with schizophrenia. We will discuss in sequence the monitoring of first- and second-generation antipsychotics, as well as the somewhat unique case of clozapine, with the goal of providing clear and concise recommendations to the clinician.

First-Generation Antipsychotics

First-generation antipsychotics (FGAs) remain in wide use despite the introduction of many newer compounds over the last 20 years. Their use remains particularly common in the treatment of populations in which cost is a concern,[2] as well as in the management of psychotic agitation.[3] The effectiveness of these compounds remains limited by nonadherence as well as dose-dependent adverse effects including effects on the extrapyramidal motor system.

Given that both of these limitations can be informed by the use of TDM, it would seem that its use might be particularly appropriate in the management of patients with schizophrenia who have been prescribed FGAs. Indeed, in their 2011 consensus guidelines,[1] the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP; Workgroup for Neuropsychopharmacology and Pharmacopsychiatry) gave their highest level of recommendation to the monitoring of the FGAs haloperidol, fluphenazine, and perphenazine. In the case of haloperidol, clinical response has been shown to decrease at serum concentrations above 10 ng/mL, with levels of 15 ng/mL being associated with more adverse effects, particularly serum prolactin.[4] Maintenance of serum concentrations within the recommended window of 1–10 ng/mL can prove particularly challenging in patients transitioning from oral to depot medication, as well as in those taking concomitant medications that interfere with the rate of metabolism of cytochrome P450 (CYP) 2D6, including the commonly prescribed antidepressants fluoxetine, paroxetine, and duloxetine. A range of 1–10 ng/mL, with similar concerns to those referenced for haloperidol, is recommended for the monitoring of fluphenazine. Perphenazine, an FGA with a relatively low incidence of extrapyramidal side effects, has been shown to be most effective at concentrations of 0.6–2.4 ng/mL, with such side effects rarely occurring at concentrations below 5 ng/mL.[5]

Second-Generation Antipsychotics

Second-generation antipsychotics (SGAs) are among the most widely prescribed compounds in the United States. Despite this fact, routine monitoring of their serum concentrations in patients

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with schizophrenia has yet to enter common clinical practice. The AGNP Consensus Guidelines[1] grant their highest level of recommendation to the commonly prescribed SGAs risperidone and olanzapine, with frequently used drugs such as quetiapine and aripiprazole achieving the second level of recommendation. Of all of the SGAs, risperidone has the most supporting evidence for a direct relationship between serum concentration and clinical response,[6] with the AGNP recommending combined levels of risperidone and its active metabolite 9-OH-risperidone at 20–60 ng/mL. Levels above 120 ng/mL have been shown to correlate with the development of parkinsonian symptoms and elevated prolactin. At least 1 study has suggested that olanzapine levels over 23 ng/mL (AGNP recommended range, 20–80 ng/mL) are associated with clinical response.[7] Olanzapine levels are also influenced by patient smoking habits through induction of CYP1A2, and thus changes in such habits may change clinical outcomes with no adjustment in dose taking place.

Quetiapine (recommended range, 100–500 ng/mL) and aripiprazole (150–500 ng/mL) do not have the same level of evidence supporting TDM as do risperidone and olanzapine, although in each case at least 1 study has suggested an ability to predict clinical response based on serum concentration,[8] and nonadherence with both medications is sufficiently frequent that routine monitoring may provide the ability to intervene clinically and prevent relapse.

Clozapine

Clozapine, the only compound approved for the management of treatment-refractory schizophrenia, has had its use in the United States limited by serious side effects, both idiosyncratic and dose dependent. The monitoring of clozapine is of particular importance given the severity of illness of many of the patients requiring this medication as well as the risk of seizure at particularly high concentrations or with rapid shifts in concentration. The AGNP again grants its strongest level of recommendation to the monitoring of clozapine, with a recommended therapeutic range of 350–600 ng/mL. Indeed, a threshold for response of approximately 350 ng/mL is one of the more reliable findings in the literature on TDM in psychopharmacology,[9] and levels above at least 600 ng/mL (and certainly 1,000 ng/mL) are routinely associated with an increased risk of seizure.[10] Additionally, as smoking is well known to lower serum clozapine levels through induction of CYP1A2, levels are likely to vary considerably in individual patients at different points in the course of treatment, particularly during the transition to the outpatient setting from inpatient hospitalization. Given that blood draws are a routine part of the management of patients taking clozapine (due to the risk of agranulocytosis), regular addition of clozapine serum levels to some routinely ordered blood tests should constitute a mainstay of treatment.

Summary and Recommendations

The routine monitoring of serum levels of antipsychotic drugs in patients with schizophrenia has yet to enter common clinical practice despite a substantial body of evidence and expert consensus guidelines. In the cases of the compounds haloperidol, fluphenazine, perphenazine, risperidone, olanzapine, and clozapine, drug monitoring can provide valuable information about adherence, the likelihood of clinical response, and the potential development and reduction of adverse effects. Although routine drug monitoring may not be necessary in patients who are clinically stable and not experiencing adverse effects, major clinical decisions, including the decision to increase doses or switch medications due to lack of efficacy and the decision to stop oral augmentation of long-acting injectable medication, should be informed by serum concentrations of the drugs in question. Concerns about potential nonadherence or treatment-emergent adverse effects can also be clarified through direct monitoring of drug levels. The authors recommend assessment of blood drug levels in patients with schizophrenia taking these medications in such situations. Trough levels should be assessed at steady state, that is, at least 4 half-lives after initiation or change in dose.[1] Although such tests may not be readily available in all clinical environments, it is likely that, with an increase in the appropriate usage of and demand for these tests in the psychiatric community, their availability will increase accordingly.

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