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A review of a recently published guidelines' "strong recommendation" for therapeutic drug monitoring of olanzapine, haloperidol, perphenazine, and fluphenazine

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Abstract

Introduction: In addition to clozapine, there is a growing body of evidence that supports therapeutic drug monitoring (TDM) for additional antipsychotics commonly used in the United States.

Methods: The Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP) published TDM guidelines for several psychiatric medications. Sources were identified that the authors used to establish therapeutic reference ranges for haloperidol, fluphenazine, perphenazine, and olanzapine—4 antipsychotics commonly used in the United States with a "strong recommendation" for TDM. The sources were then reviewed for content and appropriateness for utilization in establishing the reference ranges.

Results: Olanzapine had 15 citations, haloperidol had 9, perphenazine had 4, and fluphenazine had 2. The studies' methods were reviewed along with the proposed therapeutic reference ranges.

Discussion: Several limitations of the guidelines were identified. Reference ranges were suggested based on studies of patients with various diagnoses; some patients had an acute exacerbation, and others were in a maintenance phase. An additional publication was identified that reviewed similar (and additional) TDM studies; those conclusions were in slight contrast with those of the AGNP guidelines. In the future, guidance should be given to those looking to conduct TDM studies to standardize methods and make meta-analysis of this data more feasible.

Keywords: TDM, therapeutic drug monitoring, plasma concentrations, olanzapine, haloperidol, perphenazine, fluphenazine

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Introduction

In 2004, the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP) published therapeutic drug monitoring (TDM) guidelines for a number of psychiatric medications with the most recent update in 2017.[1] There are many medications available for the treatment of neuropsychiatric disorders, but the clinical benefit they provide is still far from optimal. There is growing evidence that improved application of currently existing medications may further benefit patients. Therapeutic drug monitoring is a growing area of health care that may help clinicians optimize treatment of their patients.[1]

Clozapine is an antipsychotic that has established trough blood concentrations that have been reviewed elsewhere.[2,3] However, clozapine is not the only antipsychotic with data supporting a therapeutic range; according to the AGNP guidelines, olanzapine (OLZ), haloperidol (HAL), perphenazine (PER), and fluphenazine (FLU) are antipsychotics regularly used in the United States that also have "level 1" evidence (ie, "strong recommendation") for TDM.[1] The purpose of this article is to review the

literature included in the AGNP guidelines for the aforementioned antipsychotics.

Methods

The AGNP TDM guidelines were reviewed to identify the sources the authors used to establish therapeutic and toxic reference ranges for the 4 antipsychotics commonly used in the United States with a "strong recommendation" to use TDM.[1] The sources' methodologies were then reviewed to determine how reference ranges were established.

Results

Olanzapine

The largest review of OLZ TDM studies was a systematic review published by Bishara et al[4] in 2013. This review included 10 studies that were analyzed for a dose-response relationship, which showed that there was minimally greater improvement for doses >10 mg/d. In addition, a dopamine 2 receptor (D2) occupancy-dose relationship was evaluated in 6 studies. A plot of striatal D2 occupancy versus dose showed that 12 mg/d occupies about 65% of D2 receptors. It has been proposed that striatal D2 receptor occupancy thresholds in schizophrenia need to be 65% for effect, 72% for hyperprolactinemia, and 78% for extrapyramidal symptoms (EPS).[5] Finally, 15 studies were evaluated to determine a dose-to-plasma level (PL) relationship.[4] A linear relationship was realized between dose and PL. It was concluded that patients have a more favorable response at 10 to 15 mg/d but that doses may be increased >15 mg/d in those whose PL are <20 ng/mL and have not achieved a favorable response. Notably, there were studies[6-9] included in this review that were also separately cited by the AGNP guidelines.

Two studies[6,10] examining OLZ long-acting injectable (LAI) in the maintenance phase of schizophrenia/schizoaffective were included in the guidelines. The first was a fixed-dose positron emission tomography (PET) imaging study of 14 patients who were stabilized on oral OLZ (5 to 20 mg/d) for 4 weeks. Dopamine 2 receptor occupancy was measured along with trough OLZ concentrations to obtain a baseline value; all patients were then transitioned to 300 mg OLZ LAI every 4 weeks for 6 months. The mean D2 occupancy was 69.1% ± 15.2% at baseline, the corresponding mean oral dose was 15.2 ± 4.8 mg/d, and PL was 37.4 ± 31.2 ng/mL. Over the study period, it was found that PL of OLZ LAI was associated with D2 receptor occupancy as expected in a curvilinear manner ($r = 0.76$, $P \leq .001$). Depot injection of OLZ LAI 300 mg every 4 weeks resulted in mean steady-state plasma concentrations of 20.3 ± 11.2 ng/mL and mean D2 occupancy approximately 60%. Some patients on the LAI required oral supplementation, but that need diminished when occupancy ≥60% was attained.[6] In the other study, 25 patients were studied to determine clinical efficacy and tolerability of OLZ LAI in relation to PL and clinical outcome in the maintenance phase of schizophrenia. Over 9 months, all patients received either 210, 300, or 405 mg every 4 weeks. Plasma levels ranged from 4 to 78.9 ng/mL; data showed that steady state was reached after the fourth injection, correlated with the maximum reduction in brief psychiatric rating scale (BPRS) and positive and negative symptom scale (PANSS) scores. Those who had less PL variation showed greater improvement in BPRS score ($P = .01$). To the authors' knowledge, this was the first study to assess clinical outcome in relation to PL of OLZ LAI.[10]

Several other studies were conducted in patients with schizophrenia on oral OLZ. One such study[11] was a concentration-dose (C/D) ratio study that found a significantly higher C/D ratio for women versus men (2.25 vs 1.62 ng/mL/mg, $P < .01$) and for nonsmokers versus smokers (2.87 vs 1.25 ng/mL/mg, $P < .001$). Additionally, in patients who reported side effects, the OLZ concentration was 22% higher than those who did not ($P < .05$), and patients who were taking carbamazepine had a 71% lower C/D ratio than those not on the medication. Another study[12] evaluated OLZ and interactions with comedication. The authors found a linear relationship between dose and PL ($P < .001$), and PL were higher in nonsmokers than in smokers ($P = .001$); age and sex had no influence on PL. A significantly higher OLZ PL was observed with fluvoxamine ($P < .001$), and a lower PL was observed when administered with trimipramine ($P = .013$) and lithium ($P = .016$).

Two studies[13,14] evaluated OLZ PL in adults with acute schizophrenia. In the first, patients were given OLZ 5 to 30 mg/d once a day in the evening. A break point of 23 ng/mL that separated responders from nonresponders (ie, 20% more patients responded when their PL was ≥23 ng/mL) was identified.[13] In the other study,[14] the mean dose achieved was 15.27 mg/d, and the mean corresponding PL was 33.15 ng/mL. Clinical improvement as rated by the BPRS and PANSS scores was correlated in a curvilinear manner with OLZ PL.

Two studies[15,16] specifically looked at the impact of genetic variation in the pharmacodynamics of OLZ. The first[15] was a pharmacogenomics study conducted in Japan that found no effect of various functional polymorphisms on OLZ PL. Improvement in total BPRS scores was not correlated with PL either; however, improvement in suspiciousness, hallucinations, and blunted affect were significantly correlated with plasma OLZ concentration. A follow-up study to the Clinical Antipsychotic Trials of

Intervention Effectiveness (more commonly known as CATIE) schizophrenia trial was also published[16] that evaluated the effect of the CYP3A43 genotype. What was initially thought of as a racial difference was found to be explained by genotype difference in which AA carriers had a 37% higher clearance than GG carriers, which translated into a 48% lower trough PL (25 vs 37 ng/mL). It should be noted that a higher proportion of African Americans are AA carriers compared to whites (67% vs 14%).

Great intraindividual variability (up to 10.7-fold) in OLZ PL was found in patents 10-20 years old, which may limit the use of TDM in this population.[17]

One study[18] looked at PL in relation to antimanic effect in those with "*DSM-IV* mania." In a subgroup of 8 female patients, the authors found a significant relationship between antimanic effect and OLZ PL at 2 weeks of therapy on OLZ 20 mg based on the Bech-Rafaelsen mania scale (Spearman correlation coefficient = –0.74, $P = .05$) but not as rated by the Young mania rating scale. The mean plasma concentration of OLZ at 2 weeks was 29.9 ± 13.5 ng/mL.

Another study[19] described OLZ TDM quantification methods but did not report ranges.

Based on the included studies, the AGNP guidelines[1] denote the reference range for plasma OLZ levels as 20 to 80 ng/mL and a laboratory alert level of 100 ng/mL.

Haloperidol

One of the most comprehensive publications reviewing TDM for HAL was a meta-analysis conducted by Ulrich et al.[20] The therapeutic window (TW) derived from the review studies was 5.6 to 16.9 ng/mL. Three-hundred two patients within the TW had an average symptom improvement of 37.4%, and 250 patients outside of the TW (below and above range) had an average improvement of 26.2%, $P < .0001$. It is also important to note that those within the TW saw greater symptom improvement than those who were above the TW as well (37.4% vs 27.8%, $P < .05$).[20]

In a 12-week double-blind study[21] evaluating the effect of "standard" (12 to 36 mg; mean = 15 mg) versus "high-dose" (10 to 240 mg; mean = 103 mg) HAL in patients with "unsatisfactory antipsychotic effect of the previous neuroleptic treatment,"(p18) there was no correlation found between plasma concentration and clinical effect or between serum prolactin concentration and clinical effect. However, there were more reported side effects in the high-dose group: drowsiness (42%), aggressive periods (25%), and seizure (8%). It should be noted that aggression resolved when the affected patients had their dose lowered by 50%.[21]

Haloperidol is a substrate of CYP2D6 (major), CYP3A4 (major), and CYP1A2 (minor).[22] In a CYP2D6 polymorphism study,[23] it was found that patients with a greater number of functional CYP2D6 alleles had lower trough HAL plasma concentrations; however, no correlation was found between plasma concentration, number of alleles, and treatment outcome/side effects.

One study[24] evaluated the effect of smoking on HAL levels. In this 2-week fixed-dose study, it was found that smokers had lower PL than nonsmokers (10.5 ± 7.0 ng/mL vs 18.1 ± 8.3 ng/mL; $P = .046$) as long as the total daily dose was <0.5 mg/kg/d.

Many PET studies have been conducted to evaluate antipsychotic effect as it relates to D2 receptor occupancy. The first double-blind PET study[25] conducted in patients on HAL found that all patients who had a 40% reduction in symptoms had at least 60% D2 occupancy. In another PET study,[26] the authors suggested a threshold for antipsychotic effect at 70% D2 receptor occupancy and a threshold for EPS more than 80%. An additional PET imaging study[27] discussed in the guidelines assessed if a derived equation could reliably predict D2 occupancy in a cohort of "mostly neuroleptic naive" (18 of 21) male and female patients (average age: 29.9 and 29.2, respectively). All patients were taking either 1 or 2.5 mg once daily; PET scans and plasma concentrations were drawn between 12 and 13 hours after the dose was given. The equation %D2 occupancy = 100 × [plasma HAL/(ED50 + plasma HAL)], where ED50 = 0.4 ng/mL, predicted D2 occupancy with a small degree of error (3.89% confidence interval = 0.45-7.33). In addition, the predicted and measured D2 occupancy levels were correlated (Pearson $r = 0.864$, $P = .003$).[27]

In an attempt to find an effective dose of HAL, a pharmacokinetic-pharmacodynamic modeling study[28] was conducted that utilized data from a number of different previous studies. In short, data from 122 patients with HAL concentrations were extracted from 7 studies and were correlated with PANSS score data from 473 people (4 different studies) with acute and chronic schizophrenia who ranged from 18 to 69 years old. Based on the pharmacokinetic-pharmacodynamic model, the oral dose of HAL needed to achieve a 30% reduction in PANSS score is 5.6 mg/d, and the corresponding plasma concentration is 2.7 ng/mL.[28]

Based on the included studies, the AGNP guidelines[1] denote the reference range for plasma HAL levels as 1 to 10 ng/mL and a laboratory alert level of 15 ng/mL.

Perphenazine

A minimum effective dose–finding study[29] was conducted in 20 patients with schizophrenia who ranged in age from 18 to 65. Every 3 months, the dose of the patients' PER LAI (not available in the United States) was reduced until symptoms appeared that were suggestive of a prodromal phase of a psychotic episode. The mean minimum effective plasma concentration was determined to be 2.92 ng/mL (range: 0.8 to 7.24 ng/mL); the authors[29] found there was no correlation between serum concentrations and side effects and that levels were so varied that TDM may not be useful as employed in this study.

A review by Van Putten et al[30] looked in depth at multiple studies of PER. In the first,[31] 34 patients with schizophrenia were randomly assigned to a low (<1.2 ng/mL) or high (2 to 4 ng/mL) PER PL. Before data was evaluated, 8 dropped out due to nonadherence; the data on the dropouts were not analyzed. After 5 weeks of treatment, it was found that patients who achieved a PL >0.8 ng/mL had a significantly better therapeutic outcome ($P = .005$); this was not elaborated on in the review. The same group of authors conducted a second study in 32 newly admitted patients with schizophrenia.[31] The purpose of this study was to examine the relationship between EPS and PER levels. In this study, 6 dropped out due to nonadherence (data not analyzed). The remaining patients received PER 12 to 48 mg/d. PER levels greater than 1.2 ng/mL were associated with increased risk of EPS ($P < .02$) and a slightly weaker treatment response that did not reach statistical significance. Based on these 2 studies, the authors concluded that the optimal range for PER was 0.8 to 1.2 ng/mL.[31] In another study,[32] investigators measured PER PL in 228 psychiatric inpatients. The mean PL was 4.6 ng/mL, and it was found that 46% of the patients had PER PL above the optimal range established by the aforementioned group of authors (0.8 to 1.2 ng/mL). Of these patients above the optimal range, 50% had EPS and 80% had a "definite" antipsychotic response. Plasma level was reduced to the optimal range in 24 of the 105 patients above the range, and EPS subsided with no alteration in response. Of the patients initially within the range, only 8% had EPS, and 86% "responded" to treatment. Of those below the range, 45% "responded" and 11% experienced EPS; in these patients, increasing PL into the optimal range improved antipsychotic response without causing EPS. These authors[32] concluded that a range of 0.8 to 2.4 ng/mL could be recommended, but no data were shown to support this range. A third group[33] treated 66 newly admitted patients of varied diagnoses with PER 0.5 mg/kg/d for 10 days. The PER levels were not significantly correlated with global ratings of psychosis ($r = -0.06$); however, when summing two BPRS items (ie, hallucinations and conceptual disorganization), a threshold of 0.8 ng/mL was confirmed to produce the highest point biserial correlation of the levels tested ($r = -0.56$, $P = .0001$). Additionally, patients treated with benztropine had a mean PL = 3.5 ng/mL, whereas those who did not had a mean PL = 2.22 ng/mL, supporting the range suggested by an earlier group of authors (0.8 to 2.4 ng/mL).[31] Based on these 4 studies, the authors of this review article recommended a therapeutic range of 0.8 to 2.4 ng/mL for PER.

In a pharmacologic profile study[34] of 54 older patients with dementia receiving PER 0.1 mg/kg/d, it was found that the mean PL was 1.5 ± 1.4 ng/mL. Neither the parent compound nor either of the 2 metabolites were associated with EPS severity/onset.

A study[35] of antipsychotic levels in postmortem blood was cited; however, this type of sampling is unreliable in determining therapeutic PLs. Based on the included studies, the AGNP guidelines[1] denote the reference range for plasma PER levels as 0.6 to 2.4 ng/mL and a laboratory alert level of 5 ng/mL.

Fluphenazine

The publication by Van Putten et al[30] also outlines a number of studies on patients taking FLU. There were 3 fixed-dose studies that examined clinical response in newly admitted patients with schizophrenia. The first was a study[36] of 29 patients receiving FLU 5 to 20 mg/d. After 2 weeks of treatment, a therapeutic range was suggested of 0.2 to 2.8 ng/mL based on 3 nonresponders above the range and 2 nonresponders (and 1 partial responder) below the range. A significant curvilinear relationship was identified ($P = .02$). The second study[37] evaluated 19 patients with schizophrenia who received the same dosing range as the first study. After 2 weeks, a mean reduction in symptoms of 59% was observed within the 0.13 to 0.7 ng/mL range as opposed to the 0.8 to 2.3 ng/mL range in which patients saw a mean improvement of 34% ($t = 3.22$, $P < .01$, 2-tailed) on the New Haven schizophrenia index. The third[38] evaluated patients with schizophrenia taking FLU 10 or 20 mg; after just over 3 weeks of treatment, there was a linear correlation between PL and improvement on the BPRS "thinking disturbance" item that occurred in the 0.2 to 4.5 ng/mL range. The first 2 studies[36,37] found more modest improvements at higher doses; this was not realized in the third fixed-dose study.[38]

In a study carried out by the review article authors,[30] 72 male veterans with schizophrenia were assigned to receive FLU 5, 10, or 20 mg daily for 4 weeks; patients were considered "markedly ill" at baseline. Logistic regression was used to measure the outcomes "global improvement" (marked or moderate improvement on clinical global impression scale) and "disabling side effects." Logistic regression for improvement and disabling side effects

were both significant, indicating that, as PL increased, more patients improved and more patients experienced side effects ($P = .015$ and $P = .0008$, respectively). Data were also analyzed to determine at what PL the maximum amount of patients improved without experiencing disabling side effects and was determined to be 0.67 ng/mL. Contrary to 2 previous studies, higher FLU PL (up to 4.23 ng/mL) were associated with greater improvement; however, close to 90% of patients had disabling side effects at 2.7 ng/mL. As far as the patients were concerned, these side effects negated or compromised the improvements in psychosis.[30]

In addition to oral FLU studies, the LAI formulation was also reviewed. These studies generally differ from acute schizophrenia studies as they focus more on relapse prevention (and use lower doses) versus treatment of acute exacerbations (higher doses). One such study[39] found that patients who relapsed had lower PLs (mean = 0.92 ng/mL) than those who did not (mean = 1.36 ng/mL). Another report[40] found a therapeutic threshold of 0.2 to 0.4 ng/mL in patients on oral FLU or the LAI formulation. In another FLU study carried out by the authors of the review,[30] PL were monitored in patients randomly assigned to receive 5 or 25 mg FLU LAI every 2 weeks. Plasma levels were measured at 3, 6, and 9 months; there was a statistically significant relationship between lower PL and psychotic exacerbation at months 6 and 9 ($P = .04$ and $P = .003$, respectively). Rates of psychotic exacerbation were relatively low above PL = 0.8 to 0.9 ng/mL, and few exacerbations occurred above 1.2 ng/mL.[30] Based on the included studies, the AGNP guidelines[1] denote the reference range for plasma FLU levels as 1 to 10 ng/mL and a laboratory alert level of 15 ng/mL.

Discussion

The AGNP Guidelines

Although the AGNP guidelines[1] are a valuable resource, there are limitations that should be mentioned. The first limitation to highlight is that a detailed description of the authors' search methods is lacking. The authors state, "literature search was conducted, primarily in PubMed and in summaries of product characteristics (SPC), and also by hand in pharmacologic and clinical chemical journals to identify TDM-related information. More than two thousand articles were assessed."[1(p12)] There is no specific search string that can be entered into PubMed to replicate their search, nor are time periods defined for the date range of publications evaluated for inclusion. Additionally, the authors mention that data were extracted and analyzed from around 1400 articles using a checklist *(drug AND concentration AND (blood OR plasma OR serum))*. This checklist is not described.

One of the most important limitations to point out is that there is no discussion of the studies and their methodology. For example, the authors[41] highlight a clozapine study conducted in an "almost optimal" manner in which three separate PL ranges were targeted; however, most of the studies in the guidelines were fixed-dose, which are considered "feasible" for evaluation of the lower limit.[1] Another limitation was the lack of a standard dosing schedule and no mention of the timing of "trough" plasma levels. Olanzapine was dosed once or twice a day depending on the study. This discrepancy may not matter as much for drugs with longer half-lives, but these variables will ultimately affect the trough PL regardless of the drug being studied. In addition to this, there is no discussion on how the reference range for each drug was ultimately decided upon based on the included studies. Not to be overlooked, many of the studies cited by the authors describe a percentage reduction in symptoms, but the scale is not specifically stated.

It is well known that postmortem redistribution is a phenomenon that complicates the interpretation of blood concentrations after death, specifically elevating the concentration above that of what would have been found premortem[42]; however, the same postmortem study is cited twice in the guidelines (once in the PER section and once in the FLU section with reference ranges well above what other studies demonstrated).[43] There is no comment from the authors on the relevance of this reference.

The guidelines include several studies that include various diagnoses. In some studies, multiple populations are studied at the same time—in 1 PER publication, patients with "manic psychosis, major depressive disorder with psychotic features, schizophrenia, and schizophreniform disorder"[30(p210)] are evaluated in the same manner. In other publications, specific populations are studied that differ from the larger whole of the literature—in 1 OLZ study, the population evaluated had bipolar disorder and were experiencing mania,[18] whereas the rest of the literature focuses on patients with schizophrenia.

Furthermore, there is no differentiation between studies on patients with schizophrenia who are experiencing an acute exacerbation versus those who are in the maintenance phase and are involved in relapse-prevention studies. One interesting finding that speaks to this is a study[43] that was conducted in patients who were stable on OLZ LAI in which trough PL were taken and observed to be less than 20 ng/mL (reference range: 20 to 80 ng/mL) in more than 50% of patients who were stable.

Other Publications

A number of other publications address the issue of antipsychotic blood concentration monitoring when it comes to its role in assessing adherence, intolerable side effects, and predicting therapeutic effect. It seems that blood concentration monitoring to assess adherence (eg, whether the patient is taking the medication at all) is agreed upon, but its role as far as evaluating safety and efficacy is debated based on the lack of well-designed studies. In a recent article,[44] it is suggested that evidence for applying TDM is established for the assessment of side effects for clozapine—and growing for quetiapine, risperidone, and olanzapine. In relation to efficacy, the authors state that there is strong evidence to employ TDM for clozapine, HAL, and PER, and evidence is limited but promising for OLZ, risperidone, and aripiprazole. This is in contrast with the AGNP guidelines,[1] which "strongly recommend" TDM for clozapine, HAL, FLU, PER, OLZ, thioridazine, and amisulpride; the guidelines do not differentiate between using TDM for side effects or efficacy.

Conclusion

The AGNP guidelines offer insight into a challenging topic. Therapeutic drug monitoring studies cited in some of the review articles discussed herein date back to the late 1970s. Over the years, methodology has improved to the point that some older studies may be considered inadequate by today's TDM-study standards. It is important that the clinician use TDM as a tool and not rely on it solely in place of good clinical judgment. Future research should be guided by previous research with accepted methodology, such as the VandarZwaag et al[41] clozapine study, in which different blood concentration ranges are targeted and maintained and then patients are assessed. Based on the aforementioned limitations, it is difficult to recommend widespread use of the proposed reference ranges. The included studies' dosing and timing of PL samplings were not clearly defined, diagnoses widely varied, and illness that were acutely exacerbated or in the maintenance phase were included together without mention of how ranges were ultimately established. Unfortunately, these guidelines may not be ready to be widely adapted based on the limitations discussed herein; however, individual studies identified by the guidelines may prove more helpful in specific situations.

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