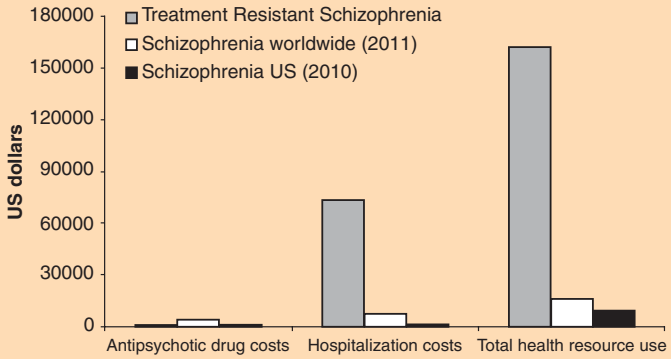
Introduction

Antipsychotics have numerous evidence-based uses in the twenty-first century, including schizophrenia spectrum and other psychotic disorders, bipolar disorder, unipolar major depression, behavioral disturbances of autism, tic disorders, and obsessive compulsive disorder [1]. The application of antipsychotic therapy in many of these conditions is adjunctive, and it may be withdrawn during less active phases of the illness. For patients with schizophrenia spectrum disorders, antipsychotics are the foundation of treatment without which the patient is at risk for relapse, and the attendant psychiatric, social, and legal consequences [2, 3]. Given the level of disability often encountered with the onset of illness, the care and management of individuals with schizophrenia exerts a significant economic toll on society [4–6]; moreover, this burden accrues most directly to families and direct caregivers in the form of financial loss compounded by stress and decreased quality of life [7, 8]. Of particular concern are the disproportionate direct and indirect costs associated with treatment-resistant schizophrenia (TRS) [4] (see Figure 0.1).

That the care costs for TRS are 3–11 times higher than for other schizophrenia patients is not surprising, but the disturbing clinical reality is that, aside from treatment resistance, there are many reasons patients fail to respond adequately to an antipsychotic, with nonadherence, underdosing, and kinetic issues playing significant roles [9]. To emphasize this point, a study of 99 schizophrenia patients deemed treatment resistant in the South London and Maudsley National Health Service (NHS) foundation clinic found that 35% had subtherapeutic plasma antipsychotic levels [10]. Real-world data such as these encapsulate the basic arguments for monitoring of antipsychotic plasma levels: antipsychotic nonadherence is common in schizophrenia patients [11]; clinicians are poor estimators of medication nonadherence [12–14]; kinetic variations or underdosing contribute to inadequate response [10]; plasma level, and not prescribed dose, is the best proxy for central nervous system antipsychotic effects [15, 16].

Figure 0.1 Healthcare costs per patient-year for schizophrenia patients from studies published 1996–2012 worldwide, for US schizophrenia patients, and for treatment-resistant schizophrenia patients (2012 USD)[4]



(Adapted from: J. L. Kennedy, C. A. Altar, D. L. Taylor, *et al*. [2014]. The social and economic burden of treatment-resistant schizophrenia: A systematic literature review. *Int Clin Psychopharmacol*, 29, 63–76.)

A Deterrents to Clinical Use of Plasma Level Monitoring

Despite multiple evidence-based reasons for therapeutic drug monitoring (TDM) of antipsychotic treatment (see Box 0.1) [17], a certain degree of nihilism exists among clinicians regarding implementation in routine care. A 2014 UK survey study of 105 London consultant psychiatrists found that most based their choice of optimum antipsychotic dose on past clinical experience with similar patients (80%) and their subjective impression of dose equivalence between antipsychotics (70%) [18]. While the majority routinely used plasma levels for clozapine (82.9%), 32.4% did not agree that TDM would improve clinical outcomes for all antipsychotics [18].

Box 0.1 Reasons to Consider Antipsychotic Plasma Level Monitoring [17]

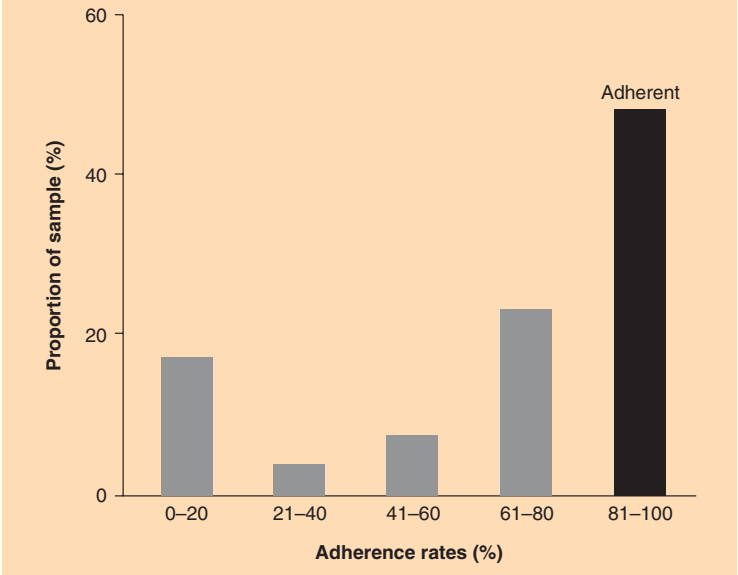
1. Uncertain adherence to antipsychotics
2. No clinical response within established therapeutic dose ranges
3. Symptom recurrence or relapse during maintenance treatment
4. Adverse drug reactions
5. Combination treatment with medication(s) with inducing or inhibiting properties

6. Genetic peculiarities for the pathways involved in the metabolism of antipsychotics (the prevalence of specific genetic variants affecting drug metabolism may vary highly in different ethnic groups, e.g., Caucasian versus Asian, middle Eastern versus the rest of the world)
7. Patients with abnormally high or low body weight or body mass index
8. Pregnant or lactating patients
9. Child or adolescent patients
10. Elderly patients
11. Patients with intellectual disabilities
12. Forensic patients or court-mandated individuals, as the treatment of this patient subgroup presents special challenges that underscore the need for tracking and mitigating nonadherence
13. Patients with pharmacokinetically relevant comorbidities, such as hepatic or renal dysfunction and severe cardiovascular disease (affecting hepatic and renal blood flow)
14. Patients with acute or chronic inflammatory conditions and infections
15. Postoperative care for patients undergoing restrictive gastrointestinal resection or bariatric surgery
16. Switching between the original preparation and generic forms of antipsychotics due to potential therapeutic equivalence differences, as well as related adherence aspects
17. Switching between oral antipsychotics and LAIs
18. Pharmacovigilance programs
19. Research

As alluded to above, and to be discussed extensively in Chapter 4, antipsychotic nonadherence has been recognized as inherent to schizophrenia for over 50 years [19, 20], yet clinicians have difficulty estimating the extent of this problem. The magnitude of nonadherence with oral antipsychotic therapy is illustrated in Figure 0.2. These data are derived from a study of 52 outpatients with a schizophrenia spectrum disorder, stabilized on the current oral antipsychotic dose for 3 or more months, who were enrolled in an adherence study [21]. Although these subjects knew they were being scrutinized as part of a study, only 48% managed to take 80% or more of their oral doses over 4 weeks, contrary to what one might assume for a stable group of schizophrenia outpatients. The data from the South London and Maudsley NHS foundation sample of 99 supposedly treatment-resistant patients being proposed for clozapine treatment represents one of many publications documenting the disconnect between clinician assessment of oral antipsychotic adherence and verified adherence using pill counts, plasma levels, or electronic devices such as the Medication Event

Monitoring System (MEMS): a medication bottle cap with a microprocessor that records each bottle opening [22].

Figure 0.2 Rates of adherence in stable schizophrenia patients monitored over four weeks [21]



(Adapted from: G. Remington, C. Teo, S. Mann, *et al*. [2013]. Examining levels of antipsychotic adherence to better understand nonadherence. *J Clin Psychopharmacol*, 33, 261–263.)

Another impediment to routine use of antipsychotic TDM has been the paucity of information succinctly summarizing dose and plasma level correlations for most antipsychotics, aside from clozapine [23]. The motivated clinician who orders a plasma haloperidol level for a patient on 10 mg at bedtime (QHS) is left to scour the literature for a method of interpreting the result. (Of note, the expected 12h trough plasma level for that haloperidol dose is 7.78 ng/ml [24, 25].) Until recently, principles for interpreting levels were not covered extensively in the literature; moreover, clinicians were often provided insufficient guidance on how to react when levels were higher or lower than expected, or the expected range of plasma level variation between sample determinations in adherent patients [26].

The published literature can also be confusing with respect to the use of antipsychotic TDM to guide treatment. Review papers often lament the limited correlation between antipsychotic plasma level and schizophrenia treatment response [27], but fail to note that many antipsychotics exhibit response thresholds based on fixed dose studies, imaging data, or both [26, 17]. Clozapine is a classic example where a consensus plasma level of 350 ng/ml has been suggested as a response threshold (also known as a lower limit of the therapeutic reference range), thereby guiding clinicians to pursue higher doses and levels in nonresponders with clozapine levels below that value [28]. While the clozapine response threshold is widely cited [26, 17], the comparable information for other antipsychotics is not given the emphasis it deserves, despite the existence of thoughtful papers aimed at elucidating TDM principles in neuropsychiatry. A leading organization spearheading these efforts has been the German Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP), whose interdisciplinary TDM group published three exhaustive reviews in 2004, 2011, and 2018 summarizing information across various classes of psychiatric medications [29, 30, 26]. Although these reviews are scholarly and were published in an English-language journal (*Pharmacopsychiatry*), the journal impact factor was not in the top 200 as of 2018, and their heroic efforts may have not been viewed by a wider audience. The growing interest in this topic, and the advent of newer technology (see Section C below), spurred the 2020 publication of a joint consensus statement by the American Society of Clinical Psychopharmacology (ASCP) and AGNP, covering the latest thinking on antipsychotic blood monitoring [17]. That this review was published in the *Journal of Clinical Psychiatry* (top-50 impact factor) hopefully represents a turning point in the clinical perception of antipsychotic TDM from a niche subject applicable only to clozapine therapy to an accepted and necessary tool in the management of schizophrenia patients.

As acknowledged by the AGNP TDM group, defining an upper limit of the therapeutic reference range is relatively easy for drugs with narrow therapeutic indices (e.g. carbamazepine, lithium, valproate), but becomes problematic for less toxic agents [26]. When adverse effects become limiting, one can utilize mathematical models to find an optimal cutpoint which maximizes the trade-off between efficacy and tolerability. Such receiver operating characteristic (ROC) curves require sufficient systematically collected plasma level data at higher levels, data that are often lacking for many antipsychotics [31]. For the AGNP guidelines, the upper limits were mostly generated by calculating expected antipsychotic-level concentrations under approved maximal doses, but the clinical reality is that many antipsychotics have sufficient evidence for use at doses beyond the initial approval range [32, 33]. Fully one-third of

schizophrenia patients respond inadequately to non-clozapine antipsychotics, yet the refusal of such individuals to start clozapine forces the clinician to consider ongoing titration of existing agents beyond their approved maximal dosages where the safety of this approach is supported by the literature, and when the patient is not exhibiting dose-limiting adverse effects. Such trials are often terminated due to tolerability, but there is a distinct subgroup of patients who tolerate higher antipsychotic doses and plasma levels without developing neurological adverse effects (e.g. parkinsonism, akathisia, dystonia) [34]. However, there is a point beyond which expectancy of response is virtually nil based on the plasma antipsychotic level, yet there is limited guidance on this point of clinical futility [35]. In certain countries, one is limited to the maximum licensed dose, so the AGNP upper limits can be implemented; however, outside of these jurisdictions, clinicians are often directed to local laboratory-reported ranges, although gross inconsistencies exist between laboratories in the methods for establishing maxima, and in the suggested maximal actual levels themselves for antipsychotics [36]. (The other major source of consternation related to laboratories, slow turnaround for plasma level results, is discussed in Section C below.)

In spite of these numerous frustrations, there is evidence that clinicians do perceive a possible benefit of antipsychotic TDM, providing hope that improved education about its use and increased availability of plasma antipsychotic level testing might meet a receptive audience. Although the survey study of 105 London consultants documented that 32.4% did not believe TDM would improve care, previous use of plasma levels during clozapine management not only predicted future TDM use ($p = 0.019$), the respondents agreed that TDM could help to minimize risk of dose-related adverse effects (77.1%), and 84.8% stated that they would use antipsychotic TDM if it were widely available [18]. A larger UK follow-up study ($n = 181$) was also optimistic regarding implementation of antipsychotic TDM: 83% of the 181 clinicians agreed that "if TDM for antipsychotics were readily available, I would use it," but prospects of future use decreased with potential barriers, negative attitudes, and negative expectations [37].

B The Economic Argument

Schizophrenia point prevalence remains relatively constant, with the global estimate of 0.28% remaining unchanged from 1990 to 2016; however, the number of individuals suffering from schizophrenia rose nearly 60% in that time due to population increases [38, 6]. While many sources traditionally cite schizophrenia prevalence rates of 1%, a 2018 analysis of 101 studies examined the variation in point prevalence, 12-month, and lifetime estimates of psychotic disorders, and the methodological issues resulting

in such variability [39]. Among studies specifically examining schizophrenia prevalence (as opposed to schizophrenia and other psychotic disorders, or 'nonaffective psychosis'), the median point, 12-month, and lifetime prevalence values were 0.35%, 0.37%, and 0.64%, respectively. Studies conducted in the general population provided higher rates than those carried out in patients receiving general health or social services ($p = 0.006$); prevalence rates were also higher for broadly worded diagnostic categories such as probable psychotic disorder ($p = 0.022$) and non-affective psychosis ($p = 0.009$). Not surprisingly, higher study quality was associated with a lower estimated prevalence of psychotic disorders ($p < 0.001$) [39].

There are now close to 21 million persons worldwide with schizophrenia, most of whom require extensive supportive resources, as only 13.5% meet criteria for functional recovery [6]. Using the outcome of years lived with disability, schizophrenia has consistently ranked fifteenth overall among 328 conditions (i.e. diseases or injuries) in the 1990, 2006, and 2016 World Health Organization (WHO) Global Burden of Disease studies, yet it carried the highest disability weight among all disorders and contributed 13.4 million years of life lost due to disability. This represented 1.7% of the total in the 2016 WHO study, a value six-fold greater than the prevalence of schizophrenia [6], and its economic burden was estimated to range from 0.02% to 1.65% of the gross domestic product [40]. For the United States (US) alone, the combination of direct healthcare costs, direct non-healthcare costs (law enforcement, homeless shelters, healthcare training, and research), and indirect costs (productivity loss from disability, premature mortality, caregiving) was estimated at $155.7 billion for 2013 [5]. The largest components were excess costs associated with unemployment (38%), productivity loss due to caregiving (34%), and direct healthcare costs (24%).

It is with this vast economic toll in mind that one can begin to appreciate the value of antipsychotic TDM. If one assumes the US 12-month prevalence estimate is comparable to the higher value cited above (0.37%), there are at least 1 million persons with schizophrenia in the US. A model generated in 2015 estimated that improved antipsychotic adherence could yield $1580 in annual savings *per patient* to state programs related to reductions in direct healthcare and criminal justice costs (in 2013 dollars) [41]. Nationally, this would amount to over $1.5B. A 2018 review concluded: "Public payers that operate under strict annual budget constraints and have discretion over which services to cover, such as Medicaid programs and the Veterans Health Administration, may be particularly interested in incorporating plasma level measurement into the routine care of people who are either not responding to standard antipsychotic treatment or are exhibiting intolerable side effects" [42].

Antipsychotic plasma level assay costs vary widely. In the UK, a clozapine assay was £25 per sample in February 2020 at King's College Hospital KingsPath Clinical Diagnostic Pathology Service (approximately $33), while this might be $100 (or more) within the US. Even if an assay costs $150 per determination in the US, one could order 3 per year and still derive a net benefit of at least $1000 per patient annually, or $1B annually for the US as a whole. As emerging technologies reduce the assay cost, these savings will increase over time. Thus, any arguments that TDM for antipsychotics are overly expensive are not only short sighted, but wrong by any economic analysis of the value to a payer who must absorb expensive direct care costs, particularly those involving inpatient psychiatric services.

Emergence of Point-of-Care Testing

Among the greatest impediments to antipsychotic plasma level determination is the paucity of laboratories running these assays, and the need to ship specimens from the place of phlebotomy to the reference laboratory. When the distance is short to the reference lab, and the laboratory volume great, assay results might be available within 2 days of sample receipt (e.g. KingsPath lab), but in common practice the entire process may take much longer due to several stumbling blocks [43]. The foremost of these is the need to send a patient for phlebotomy when such services are not available in the mental health clinic setting. If and when the patient goes to the lab, and whether the timing of the draw can yield an interpretable result are enormous problems that delay obtaining not only a result, but a result that can actually be used. When a supposed 12h trough is obtained 19 hours after the evening dose, the clinician is left to their own devices to decide what this result means. Added to the clinician's frustration is shipping time – as the local lab may batch samples sent to the outside reference lab – and the time to run the assay and report a result back to the referring source. The possibility of making urgent decisions using antipsychotic levels in a manner performed routinely with lithium or valproate becomes practically impossible. A clinician who strongly suspects nonadherence with oral antipsychotic therapy in a symptomatic outpatient may possibly obtain a level for future use, but in the short term will be forced to employ the same options as clinicians in the 1950s: make an educated guess whether nonadherence is at play for the current episode, and plan a course of action [43].

There are, however, emerging solutions in the form of point-of-care (POC) devices employing novel technology, with the goal of improving precision application of medical information with real-time results. One such device was approved in the US on November 5, 2018 (US Food and Drug Administration [FDA] 510(k)

Number K181288) for total white blood cell and absolute neutrophil counts, and includes a system created by the manufacturer to facilitate use in clozapine-treated patients (www.athelas.com). Using a finger stick rated less painful than traditional venipuncture, this device can be operated by any trained clinical personnel and provides results within 6 minutes [28, 44]. In March 2018, the first POC device was approved in the European Union (EU) for determination of an antipsychotic plasma level (www.saladax.com). The results of the test can be available as early as 1 hour from blood draw in certain settings, and within 48 hours in many others. This approval represented the culmination of many years of research into POC devices for antipsychotic TDM, starting initially with scientists at Janssen Pharmaceutica [43], and later continued by Saladax Biomedical, Inc. who completed final testing. The initial EU approval covered tests for total risperidone and paliperidone (9-OH risperidone) levels, but the platform will eventually include clozapine, olanzapine, and aripiprazole, and possibly others. As of this writing (April 2021), the company is working with the US FDA toward initial approval for total clozapine levels, with a plan to expand the suite of testing to the analytes noted above. That two POC technologies with direct application to psychiatry have been pursued in such a short time speaks not only to innovations that may significantly transform healthcare, but also to the specific technology need within the psychiatric space to improve care of the severely mentally ill. Schizophrenia management presents unique challenges, and any devices that remove barriers to treatment or improve a clinician's ability to effectively monitor and tailor antipsychotic therapy benefit all stakeholders involved in helping this patient population attain their functional goals. Precision dosing is the future of medical practice – the use of plasma levels is an important tool to add precision in the use of antipsychotic therapy [45, 46].

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