SECTION 1

Antipsychotic side effects and monitoring implications

1.1

Introduction

Poison is in everything, and no thing is without poison. The dosage makes it either a poison or a remedy.

Paracelsus, Swiss physician, alchemist, and botanist, 1493–1541

Those who say that nothing but the complete safety of drugs will suffice demand the impossible: a drug without side effects is probably an ineffective one.

Sir Derek Dunlop, MD, FRCP, First Chairman
of the UK Committee on Safety of Drugs

A history of side effects

The pharmacological era of dopamine D_2 blockade as the cornerstone of the management of psychoses has its beginnings in the late 1930s with the observation that promethazine, a phenothiazine, prolonged anesthetic sedation. The search for similar agents eventually led to the development of chlorpromazine, which, in the early 1950s, was found to potentiate anesthesia, diminish arousal and locomotion, and produce sleep or indifference, features that eventually came to define the term neuroleptic [1]. Early experience with chlorpromazine in asylums used low doses where it was found to have remarkable calming effects and good tolerability. However, as experience grew and doses increased to 500 mg/day and higher, its remarkable antipsychotic effects became increasingly recognized, bringing a new level of excitement and anticipation to the field of psychiatry [2]. Eventually, clinical experience with chlorpromazine in Europe, Canada, and the USA revealed it to be more than just a calming and sedating agent but also to have ameliorating effects on the cardinal symptoms of psychosis [3]. This started the current era, which is nearing its 60th year, of treating psychosis and mania with dopamine D_2 blockers.

Since the introduction of chlorpromazine, dozens of other antipsychotics have been developed including several other phenothiazines (e.g. thioridazine, mesoridazine, fluphenazine, perphenazine, trifluoperazine), thioxanthenes (e.g. thiothixene, flupenthixol, zuclopenthixol), butyrophenones (e.g. haloperidol), benzepines (e.g. loxapine, clozapine, zotepine) and their structural relatives olanzapine and quetiapine, as well as molindone, pimozide, risperidone and its metabolite paliperidone (9-hydroxyrisperidone), ziprasidone, and aripiprazole. Shortly after its introduction, chlorpromazine was referred to as a "double-edged therapeutic weapon" reflecting its favorable effects in psychoneuroses and psychoses and the early recognition of its frequent and sometimes fatal side effects [4–6]. By 1956, side effects such as sedation, pallor, tachycardia, hypotension, dry mouth, and constipation were well known and almost expected. Serious and fatal cases of pyrexia, skin eruptions, seizures, hepatitis, and agranulocytosis had also been reported. Reversible and irreversible movement disorders were recognized as a class effect shortly thereafter and this had a profound effect on the perception of the safety of neuroleptics [7,8]. Moreover, it gave priority to the importance of routine assessment and monitoring of patients taking antipsychotics long term [9,10].

For approximately 30 years, prescribing an antipsychotic meant using a drug that produced dose-dependent prolactin elevation and extrapyramidal side effects (e.g. parkinsonism, acute dystonia,

akathisia) and risked irreversible movement disorders including tardive dyskinesia, dystonia, and akathisia. Prolonged use of high-potency dopamine D_2 blockers (e.g. haloperidol, fluphenazine), especially when used at higher doses, appeared to cause these problems, including neuroleptic malignant syndrome, more often. The alternative of using low-potency agents (e.g. chlorpromazine, thioridazine) carried several additional concerns, including excessive sedation, syncope, hepatitis, cataracts, and seizures [4,5,11]. Over time many prescribers defaulted to the mid-potency agents hoping to find an acceptable compromise (e.g. loxapine), but it was not until clozapine's unique pharmacological and clinical properties were re-assessed and better understood in the late 1980s that new, quite different options were developed in earnest. The return of clozapine in 1989 to the international marketplace provided prescribers and patients with a welcome option of greater effectiveness with little or no risk of movement disorders, of early or late onset, but at the price of higher rates of other serious adverse effects (e.g. agranulocytosis, seizures) [12]. Its greater effectiveness, apparent advantages on negative symptoms and cognitive deficits of schizophrenia, low rate of movement disorders, and unique findings in animal studies were noted to be atypical, and with that a new nomenclature and method of classifying antipsychotics was born. However, when applied to other, newer antipsychotics, the term atypical has been diluted to mean a drug with a lower risk of extrapyramidal side effects and tardive dyskinesia. While every antipsychotic to be marketed since 1990 has been classified as atypical, the term "second generation" seems to be more fitting and carries fewer potentially misleading connotations [1].

The basis of what makes clozapine uniquely effective remains a pharmacological mystery. It has been proposed that its lower risk for movement disorders, along with other second-generation agents, is a result of greater affinity for blocking serotonin (5-hydroxytryptamine, 5-HT_2) receptors compared with dopamine D_2 receptors [13]. Others have found that dopamine D_2 receptor binding properties of antipsychotics, specifically how loosely the drug binds to the receptor as measured by its dissociation constant (K_D), more precisely predict their atypical clinical profile [14]. Antipsychotics with relatively high serotonin 5-HT receptor blocking effects include clozapine, loxapine, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone [15]. Remoxipride is classified clinically as a second-generation antipsychotic and does not have a high affinity for serotonin receptors, whereas loxapine does but is not considered atypical. Antipsychotics that rapidly dissociate from dopamine D_2 receptors include amoxapine, amisulpride, aripiprazole, clozapine, quetiapine, paliperidone, and remoxipride [16]. Slow to dissociate are chlorpromazine, haloperidol, loxapine, olanzapine, and risperidone. Olanzapine, an extensively prescribed second-generation agent, may owe its lower propensity for parkinsonism to its potent antagonist action at muscarinic receptors. Risperidone is considered to be a dose-dependent second-generation agent, in that it loses its atypical features when dosed above 6 mg/day in adults. Aripiprazole merits special mention as it is the first clinically useful antipsychotic that is not a full antagonist at the dopamine D_2 receptor. Its actions are functionally selective, including antagonist, partial agonist, and agonist, depending on the cell type and function examined [17]. This likely explains its generally low but not absent propensity to cause extrapyramidal and tardive movement effects [18].

New concerns with the second-generation takeover

The development of the second-generation antipsychotics had a profound effect on antipsychotic prescribing. In a few short years, they became not only the agents of choice but also greatly expanded the use of antipsychotics. Off-label use in mood, anxiety, sleep, personality, and impulse control disorders raced ahead of approved new indications by regulators. Across the lifespan, more people today are prescribed antipsychotics than at any time in the past [19–22]. Given this, it comes as no surprise that, in 2008, antipsychotics became the leading revenue generators for their manufacturers, more so than lipid regulators, proton pump inhibitors, and antidepressants [23]. The rapidity of the nearly complete abandonment of the conventional or first-generation antipsychotics is an indicator of the long-standing safety and tolerability

concerns with these agents, especially tardive dyskinesia and other potentially irreversible movement disorders. However, the switch has had several consequences, some less foreseeable than others.

Over time, as clinical and research experience with the second-generation antipsychotics accumulated, their negative effects on metabolic and cardiovascular indicators became increasingly obvious. This is particularly unsettling considering that patients for whom antipsychotics are primarily indicated tend to be at much higher risk for obesity, dyslipidemia, hypertension, hyperglycemia, diabetes, and major adverse cardiovascular events such as myocardial infarction, stroke, and sudden cardiac death, and have a markedly reduced expected lifespan, all independent of drug therapy [24–30]. One study estimated that 59% of the excess of deaths in schizophrenia were due to natural causes, led by cardiovascular disease, as compared with 28% due to suicide [31]. Prior to the widespread use of second-generation agents, the risk of dying due to cerebrovascular, cardiovascular, and endocrine causes was found to be two to three times higher in bipolar patients [28]. With schizophrenia, cardiovascular mortality was approximately two times higher, and the rates of ventricular arrhythmias, heart failure, stroke, and diabetes were 1.5 to more than two times that of the general population [29]. It is anticipated that the switch to and expanded use of second-generation antipsychotics will further elevate these risks in adults [32,33].

Although the risk for these prevailing concerns is higher with second- than with first-generation antipsychotics, it should be noted that risk varies within both classes. With the second-generation antipsychotics, clozapine and olanzapine have been identified as most problematic in this regard, while the concerns with risperidone and quetiapine are more moderate, and the more recently introduced ziprasidone and aripiprazole appear to be the safest options, at least in terms of effect on weight and lipids [1,24,34]. Of the first-generation antipsychotics, the low-potency phenothiazines and thioxanthenes are associated with the greatest concerns, while high-potency dopamine D_2 blockers tend to have relatively neutral effects [1,24].

Furthering the concerns about the short- and long-term safety of antipsychotics were the findings of a twofold increased risk in sudden cardiac death across all agents and an increase in overall mortality in elderly patients with dementia [35,36]. A pooled analysis of the safety data collected from 17 randomized controlled trials of second-generation agents in elderly patients with dementia revealed a 60–70% increase in total mortality. At an average follow-up of a mere 10 weeks, the mortality rate with the second-generation antipsychotics was 4.5% compared with 2.6% with placebo. This led to new warnings related to the safety of this class of antipsychotics in the elderly [37]. Several complementary observational studies comparing the risk of death between elderly users of first- and second-generation agents have consistently found that first-generation agents are no safer than the second-generation antipsychotics [38–40]. These findings led regulatory authorities to extend the warnings of increased mortality in the elderly to apply to all antipsychotics [41].

Inadequate medical care for people with mental illness

A positive effect of these new concerns is the enhanced attention and interest given to the overall health of people with chronic psychiatric disorders and to the quality of their healthcare [42]. Quality of care has generally been found to be below that of the general population, especially for people with schizophrenia and substance use disorders. This is a result of several factors related to mental illness, such as greater reluctance to seek or accept medical care and advice, and to service access and delivery [43]. In one study of US veterans with diabetes, the odds of having poor glucose and poor lipid control was increased by 17% and 20%, respectively, in people with mental illness compared with those without, and they were 38% more likely to have had no diabetic monitoring in the previous year [44]. Another study found alarming disparities in the care of patients with mental illness who had experienced an acute myocardial infarction. Compared with people without a mental disorder, they were 20% less likely to

be admitted to hospital, 13% less likely to receive reperfusion therapy, and 25% and 32%, respectively, less likely to undergo percutaneous transluminal coronary angioplasty or coronary artery bypass grafting [45]. In a related study, rates of reperfusion and treatment with beta-blockers and angiotensin-converting enzyme (ACE) inhibitors in people with schizophrenia were reduced by 52%, 25%, and 9%, respectively, and 1-year mortality was increased by 34% [46]. Preventive medical services have also been found to be less available to people with major psychiatric disorders [47]. These and other findings have stimulated numerous initiatives to improve the physical healthcare of people with mental illness, including the development of this book.

We were disappointed but not surprised to learn that our patients taking antipsychotics long term, who were known to be at increased risk for metabolic and cardiovascular disease [48], were not being routinely assessed, screened, and monitored for modifiable cardiovascular risk factors. We retrospectively reviewed all outpatient records and emergency visits of 99 randomly selected mental health clinic adult patients to identify what was being monitored and how often. Reflecting the main concerns with contemporary antipsychotic prescribing, and knowing that our patient population is at markedly increased risk for cardiovascular morbidity and mortality, we were primarily interested in weight, body mass index (BMI), waist circumference, smoking status, cholesterol, fasting plasma glucose, blood pressure, and any other evidence of metabolic or cardiovascular disease [49]. To provide some context, we looked for the same information in the outpatient charts of HIV clinic patients at our hospital, another group known to be at higher risk of cardiovascular disease [50]. Based on the information available in the mental health patients' charts, we were able to determine the 10-year coronary artery disease (CAD) risk in only 28% and it took over 2 minutes on average to find this information. In contrast, the better-organized HIV clinic charts had the needed information 90% of the time and it took a mere 18 seconds to find it. We determined that, although our patients are known to be at high risk for diabetes and cardiovascular disease, the importance of this knowledge was not reflected in our charting practice or charting organization. The sweeping change in prescribing from first-generation antipsychotics, well known for their risk of movement disorders, to second-generation agents, with their high profile metabolic and cardiovascular risks, has not been matched by changes in how patients are being monitored. Change, in this regard, is needed urgently. Our experience is not unique. Evidence of suboptimal screening, assessment, monitoring, and management of the physical health of patients with mental illness is extensive [51–54].

First-generation antipsychotics: down but not out

Concerns regarding the adverse effects of the second-generation antipsychotics on physical health have also stimulated a re-examination of the role of first-generation antipsychotics. Several well-designed non-pharmaceutical industry-sponsored randomized controlled trials and systematic reviews have helped to clarify to what extent the older and newer antipsychotics differ in terms of important clinical outcomes [55–58]. The findings of similar effectiveness, tolerability (although with differing side-effect profiles), and effect on quality of life have supported a modest return of the first-generation agents from the brink of extinction.

> Slowly, haltingly, as time goes by, the real facts about any drug emerge into full view [59].

The most recent and most comprehensive systematic review provoked Tyrer and Kendall to comment, "Antipsychotic drugs differ in their potencies and have a wide range of adverse-effect profiles, with nothing that clearly distinguishes the two major groups. Importantly, the second-generation drugs have no special atypical characteristics that separate them from the typical, or first-generation, antipsychotics. As a group they are no more efficacious, do not improve specific symptoms, have no clearly different side-effect profiles than the first-generation antipsychotics, and are less cost effective" [60]. They state that a range of antipsychotics are needed for good clinical practice due to

individual variances in response and that all antipsychotics are associated in different ways with serious adverse effects that require monitoring. Others have similarly promoted a more balanced approach to the use of first- and second-generation agents than exists today and in doing so advocate increased use of older agents [61]. However, this presents a challenge. For over a decade, the first-generation agents have fallen into disuse. Experienced clinicians have lost some of their skills in treating patients with these agents and newer practitioners have little or no experience with them.

Antipsychotic monitoring in the twenty-first century

Before second-generation antipsychotics were developed, monitoring patients taking antipsychotics required the skills of a neurologist more so than an internist. The focus of monitoring was in the detection of parkinsonism, akathisia, dystonia, and tardive dyskinesia. Several scales were developed to help clinicians reliably detect and measure these drug-induced movement disorders and were standards in the training of psychiatrists and care of patients (e.g. the Simpson Angus Scale for extrapyramidal symptoms, the Abnormal Involuntary Movements Scale [AIMS] for tardive dyskinesia, and the comprehensive Extrapyramidal Symptom Rating Scale) [62]. Other adverse effect measurement instruments, such as the UKU side-effect rating scale, were developed to assess more comprehensively the side effects of older antipsychotics [63].

With the change to second-generation antipsychotics, the urgency of monitoring for movement disorders quickly diminished and has been replaced by concerns about the development or exacerbation of cardiometabolic risk factors. However, despite numerous appeals to improve the medical management of patients taking antipsychotics, a switch in effective, safety-oriented monitoring practices has been slow to evolve [42,54,64]. Several surveys have revealed a persistent gap between the awareness of what should be monitored and actual performance [54]. Moreover, it appears that only a small minority of patients are being monitored according to published recommendations for metabolic and cardiovascular adverse effects, despite acknowledgement that doing so is important and not particularly difficult [49,65–67].

The wide-ranging and consistent findings of inadequate monitoring practices are not due to a lack of guidance. Several sets of high-profile, widely accessible monitoring recommendations for contemporary antipsychotic side effects have been available for over 5 years. In early 2004, a joint consensus statement that provided clear guidance on how to monitor for weight gain, dyslipidemia, and diabetes in patients taking antipsychotics was published by the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity [68]. Later in the same year, a broader set of recommendations based on the proceedings of the Mt. Sinai Conference, which was a consensus meeting of psychiatrists and experts in obesity, disease prevention, diabetes, cardiology, endocrinology, and ophthalmology held in October 2002, was also published [64]. Monitoring recommendations covered weight gain, diabetes, dyslipidemia, QT prolongation, hyperprolactinemia and sexual dysfunction, extrapyramidal side effects, tardive dyskinesia, cataracts, and myocarditis.

So, what does it take to ensure that patients taking antipsychotics are assessed and monitored appropriately? Druss has warned that there is no one-size-fits-all approach to resolving this issue [69]. Instead, he supports the advice from the Institute of Medicine, which encourages the adoption of models that can most easily be built into the existing organizational structure [70]. For clinicians working relatively independently, a change in referral and documentation practices is likely to augment efforts to improve patient monitoring. Referral of patients to primary care services with a clearly articulated request to monitor the patient's physical health can mitigate the burden of doing so alone. For systems with greater opportunity to integrate mental health, primary care, and other medical services, especially when a multidisciplinary approach already exists, there is greater potential for meeting guideline recommendations for monitoring and as a result improving patient outcomes [71]. This has been demonstrated in a

randomized trial of an integrated model of the primary medical care of patients with severe psychiatric disorders [72]. In this model, improved communications, via phone calls, emails, and in-person meetings, among clinic staff and patients was emphasized and considered critical for success. Even though solutions need to be implemented at the level of the clinician or clinic, health-service administrators and policy makers need to facilitate and support the needed improvements. Without their broad-reaching and enduring support, the many personal efforts, team initiatives, and demonstration projects cannot be expected to have long-lasting effects, especially as they have not done so to date.

Of critical importance for any clinician or health team is to develop standards and processes that ensure systemic assessment, monitoring, and management of potentially reversible medical risk factors, including smoking, dyslipidemia, glucose intolerance, obesity, and hypertension [73]. In parallel, methods of detecting, monitoring, and managing other treatment-related adverse effects, for example movement disorders and hyperprolactinemia-related adverse effects, need to be reviewed and revitalized.

It is also critically important to emphasize the roles of patients and caregivers who are important partners of the monitoring team. This requires effective communication, education, and use of tools to facilitate efficient and accurate assessment of treatment response and tolerability. Patient-oriented education and monitoring tools, such as Med Ed©, which encourages documentation of side effects and treatment response as well as facilitating open communications among patients, caregivers, and members of the treatment team, are simple yet very effective at promoting and supporting effective monitoring [74].

To support the safe and effective use of antipsychotics, especially when used long term, clinicians need to work within a system that supports regular follow-up and monitoring. Establishing a new standard of care in this regard requires planning; personal, professional, and health-team development; effective implementation strategies; and ongoing evaluation. As such, it needs the contribution of effective-change agents and willing clinicians. An integrated, collaborative approach is a must [75].

The change in antipsychotic prescribing preferences and the renewed attention to their adverse effects provides the opportunity for mental health teams to re-examine how they detect and monitor antipsychotic-related adverse effects. Instead of refocusing on the contemporary issues of cardiac and metabolic risk factors, a more comprehensive approach is recommended, one that ensures that patients are being monitored for all potential treatment-related adverse effects [64]. This book was developed to support healthcare practitioners in achieving this goal.

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