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Review Article

Historical perspectives on tardive dyskinesia☆

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ABSTRACT

Tardive dyskinesia (TD) is a persistent hyperkinetic movement disorder associated with dopamine receptor blocking agents including antipsychotic medications. Although uncertainty and concern about this drug side effect has vacillated since its initial recognition 60 years ago, recent commercial interest in developing effective treatments has rekindled scientific and clinical interest after a protracted period of neglect. Although substantial research has advanced knowledge of the clinical features and epidemiology of TD, many fundamental questions raised by early investigators remain unresolved. In this paper, we review the early clinical reports that led to the acceptance of TD as an iatrogenic disorder and the lingering controversies that emerged thereafter. Continued research on TD as a serious adverse reaction to treatment may not only enhance patient outcomes and recovery efforts but may also provide insights into both the mechanism of action of antipsychotic drugs and the nosology and pathophysiology of idiopathic psychomotor disorders.

"The past is never dead. It's not even past."
-Requiem for a Nun, William Faulkner, 1951

1. Introduction

In the 19th and early 20th centuries, a golden era of descriptive psychopathology, scientific interest in the nosology of mental disorders combined appreciation of neurologic as well as psychiatric dimensions of psychosis [1–3]. This integrated heuristic approach was lost and largely neglected for the ensuing half century, except for isolated pockets of stalwarts [4]. After the divergence of neurology and psychiatry as distinct specialties, psychiatry became primarily an office-based discipline providing psychotherapy for patients with neuroses and problems of everyday life. Patients with severe psychotic disorders, who were often too poor, disenfranchised and disturbed for outpatient practices, were relegated literally and figuratively to the "back-wards" of the medical and scientific establishment.

Until the middle of the 20th century, the situation for patients with psychotic disorders remained grim. Without specific treatments, patients were often confined to supportive care in institutional settings. This changed dramatically with the development of effective medications, which offered patients the chance to recover and return to their communities while transforming the mental healthcare system and the field of psychiatry. Renewed therapeutic optimism fueled a revival of interest in classical psychopathology and the neuroscientific basis of psychoses. However, extrapyramidal side effects of the new drugs, such as acute dystonic reactions, parkinsonism, akathisia, and the late appearance of hyperkinetic movements were soon noted and posed a challenge to the pharmacologic revolution. Among the more serious drawbacks of the antipsychotic drugs were the delayed-onset movements of tardive dyskinesia (TD). Although the recent development of approved treatments for TD is hopeful news for affected patients, many of the controversies about TD discussed by early investigators are worth revisiting.

2. Beginnings of psychopharmacology and the challenge of TD

In the beginning, the glimmer of possibilities for the pharmacological treatment of psychosis began with reserpine [5]. Experience with reserpine, which was used to lower blood pressure, revealed a calming effect on patients. Side effects of hypotension, depression and parkinsonism proved limiting, but elucidation of the mechanism of reserpine's actions in depleting monoamines years later were pivotal in the generation of theories on the role of neurotransmitters in schizophrenia and mood disorders, which stimulated but also to some extent froze creativity and theorizing until the present day.

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Subsequently, Delay et al. [6] reported results of administering chlorpromazine to psychiatric patients based on the astute observations of their surgical colleague Laborit who was investigating phenothiazines as pre-anesthetic agents [7]. At first, the positive effects reported with chlorpromazine were primarily psychomotor including sedation, a calm and detached demeanor, reduced excitement, and slowing that resembled parkinsonian bradykinesia [8]. The idea that motor or extrapyramidal side effects were essential to recovery and signaled effective dosing, which justified the appellation "neuroleptic" [2,6,9,10], persisted until studies distinguished neurological effects from ameliorative effects on psychotic symptoms [5,8,11]. Still, one wonders whether the efficacy of antipsychotics is related more to actions on subcortical rather than cortical components of frontal-subcortical circuits [12]. Although acute extrapyramidal side effects (dystonic reactions, parkinsonism, akathisia) were common, clinicians were reassured by the fact that they were transitory and mitigated by antiparkinsonian agents or by changes in the dose or potency of antipsychotics [8,13].

A more serious challenge facing early psychopharmacologists emerged with the recognition of delayed, hyperkinetic movements that appeared to persist despite drug withdrawal [2,14]. A brief report by Schonecker in 1957 is often cited as the first known description of orofacial movements associated with antipsychotics that persisted after medications were reduced or withdrawn [15]. He described three elderly women in Germany who developed lip-smacking movements from "the first days" up to eight weeks after treatment was initiated with chlorpromazine. Movements persisted in two of the women who were followed for one to three months after drug discontinuation, and for three months in the third who remained on chlorpromazine at a reduced dose [15]. In a more extensive report in 1959, Sigwald et al. in France convincingly described delayed-onset persistent orofacial movements and distinguished them from acute movement disorders, based on "facial-bucco-lingual-masticatory dyskinesias" that persisted for up to 27 months after drug discontinuation in four elderly nonpsychotic women treated with phenothiazines [16].

Uhrbrand and Faurbye in Denmark described their experience with 33 mainly chronic psychotic patients with irreversible bucco-lingual-masticatory dyskinesias but also observed associated generalized dystonic and akathisia-like symptoms in some patients [17]. Despite drug discontinuation in 17 patients, 11 showed persistent movements over four to 22 months. They also observed that some dyskinesias first appeared or worsened after drug withdrawal. In a later report, Faurbye et al. reviewed their experience, coined the term "tardive dyskinesia", and established the essential clinical and epidemiologic features of the disorder [2,11]. Hunter et al. in England reported 13 women with chronic psychiatric illness who showed permanent, heterogeneous movements after receiving phenothiazines for several years [18].

Reports of prolonged movement disorders also appeared in the American literature; Kruse described three elderly women with persistent restless movements that persisted for three to 18 months after withdrawal of phenothiazines [19]. Druckman described more severe presentations of mixed orofacial, limb and truncal movements, including dystonia, that persisted for up to 20 months following drug withdrawal [20].

Once the core features of TD were described, a groundswell of confirmatory reports presented a problem for the nascent field of psychopharmacology. Although an increasing accumulation of research subsequently established the clinical significance of TD, which was officially accepted and sanctioned by the mid-1970s [21,22], several of the initial objections raised about the importance of TD touch upon continuing areas of uncertainty as reviewed below.

3. Questioning the significance of TD

In the decade following the initial reports, several editorials raised but also questioned the validity and significance of TD [23–28], suggesting that it had been "misrepresented" and was "not of great clinical significance". Several objections reflected a lack of knowledge about the attributes of movement disorders (which are still misunderstood and misinterpreted as voluntary or attention-seeking behaviors by uninformed caregivers and professionals even today) such as fluctuation with anxiety or distraction, disappearance during sleep and suppression by voluntary control, whereas other observers dismissed TD as self-stimulatory behaviors or the natural reaction to dry-mouth and dental conditions [23,29]. But other objections reflected puzzling aspects of TD not easily dismissed including how often it occurred, who might be at risk, whether it was reversible, its functional impact, and its differentiation from abnormal movements known to occur among patients long before the advent of psychotropic drugs.

3.1. Prevalence of TD

In an early review of case reports, Kline noted in 1968 that the majority of patients with TD were elderly in chronic care settings with long-term phenothiazine treatment, most of whom had evidence of underlying brain damage. He concluded that an "epidemic" of TD among the millions of people who received phenothiazines was "nonexistent" [23,27], echoing several reassuring editorials at that time [24–26,29].

Although Kline was correct that most cases had been described in elderly, institutionalized women, many of whom had electroconvulsive therapy, leucotomy, or dementia, this reflected a skewed, selection bias of early reports. These speculations were refuted by several reports of TD in younger patients and in non-psychotic patients with gastrointestinal disorders, pain syndromes, and depression [14,16,30–33]. (Ironically, this bias that TD is restricted to the chronic mentally ill, may once again become a concern as antipsychotics are widely marketed to an ever-expanding population of nonpsychotic patients with mood disorders and other indications, including children and the elderly, who are also at risk for TD). In subsequent years, appreciation of the extent and risk of TD became increasingly recognized; several groups reported rates of dyskinesias between 11% and 26% among psychiatric patients [11,14,34,35]. In later surveys, prevalence rates of up to 40% were reported and the relative risks of age, gender, brain damage, drug dose, duration and other treatment factors were clarified [12,32,35,36]. These early findings on the incidence, prevalence and risk factors for TD have been repeatedly strengthened and replicated by extensive epidemiologic studies in the intervening years, confirming that TD is not rare and that anyone exposed to treatment with antipsychotics is at risk [33,37,38].

3.2. Reversibility of TD

Though the efficacy of antipsychotics in reducing psychosis was a major breakthrough, the idea that treatment could produce irreversible neurologic damage was deeply troubling. Descriptions of the course and outcome of TD in early reports were variable, which led to confusion and controversy over the reversibility of TD. Variability in early reports partly reflected differences in sample populations and the length of follow-up. Most studies were conducted on chronically-ill older populations with varying durations of treatment, and which often followed patients for only brief periods [23].

Major confounding factors included whether or not antipsychotic drugs were continued, and the recognition of transient withdrawal dyskinesias [17,23,34]. The fact that TD could be masked or suppressed by antipsychotics and may first become apparent or worsen on drug withdrawal in 5% to 67% of patients was puzzling and cause for questioning the role of antipsychotics in causing TD in the first place [35,39–41]. Similarly, the fact that TD did not respond to anticholinergic drugs, unlike acute dystonic reactions and parkinsonism, also confused early observers [28,41]. Several cases were reported in which early identification of dyskinesias, after drug withdrawal or after relatively brief periods of antipsychotic treatment, resulted in rapid