Introduction: The Long and Winding Road to Tourette Syndrome

Tourette Syndrome: From Witchcraft to Pharmacotherapy

The 'maladie des tics' is currently associated with the name of the French physician who published its first scientific description, Georges Gilles de la Tourette. What is currently known as Tourette syndrome should be more appropriately referred to as 'Gilles de la Tourette syndrome' – after the full surname of the French doctor who published the first comprehensive description of this complex tic disorder. The 1885 article by Gilles de la Tourette featured a case series of nine patients sharing a triad of symptoms encompassing motor/vocal tics (involuntary movements and vocalizations), echolalia (involuntary repetition of others' words) and coprolalia (involuntary swearing). The current definition of Tourette syndrome as a complex chronic tic disorder focuses on the presence of multiple motor tics plus at least one vocal tic, whereas complex vocal tics such as echolalia and coprolalia are not included in the diagnostic criteria. However, this is only the most recent part of a long history that dates back to ancient times. The earliest written record of a possible case of Tourette syndrome might date back to Suetonius' biography of Roman emperor Claudius (in the classical world) and to the description of a priest afflicted with uncontrollable thrusting of his tongue reported in the *Malleus Maleficarum* (in the fifteenth century). It is perhaps not surprising that in the pre-scientific mystic-religious era, tic disorders were seen as a sign of a weak mind or as the effects of supernatural powers – something that could suddenly make otherwise healthy and sound individuals move and shout against their will. At around the same time, one of the first and most elegant descriptions of the involuntary nature of certain abnormal movements (tremor) was produced by Leonardo da Vinci (1452–1519): 'move their trembling parts . . . without the permission of the soul'.

Individuals with tics attracted medical attention for the first time in France at the beginning of the nineteenth century. In 1825, Jean Itard (1775–1838), director of the Royal Institute for Deaf Mutes in Paris, published the case of Marquise de Dampierre, a French noblewoman who became famous because of her involuntary movements and obscene utterances. A 1873 monograph by the famous French physician Armand Trousseau described several patients with motor and vocal tics. In 1884, British neurologist John Hughlings-Jackson published a single case report on a patient with tics seen in London. Despite these earlier publications, Georges Gilles de la Tourette (1857–1904) was the first person to characterize the various features of the condition that bears his name, thus pioneering the recognition of Tourette syndrome as a neurological disorder (Figure A). Interestingly, Gilles de la Tourette's landmark 1885 publication included a reappraisal of the

Figure A Georges Gilles de la Tourette (1857–1904).

case of the Marquise de Dampierre and briefly mentioned (in a mildly critical way) Trousseau's observations on the nature of tics. The incorporation of Gilles de la Tourette's name into the eponym was promoted by Gilles de Tourette's mentor, Jean-Martin Charcot (1825–93), who has been deservedly referred to as the father of modern neurology (Figures B and C).

According to Meige and Feindel's influential 1902 study 'Les tics et leur traitement', only a minority of persons with tics fit Gilles de la Tourette's initial description. These authors argued that most tics resulted from uncorrected infantile habits in a population with hereditary weakness. Meige and Feindel's hereditary view proved compatible with eugenics, and it also paved the way to Freudian explanations of early childhood sexual repressive conflict. The first modern clinical-descriptive stage was followed by a psychoanalytic-psychosocial stage: since the French neurologists did not have any definitive explanation for tic disorders other than a sign of degeneration, psychoanalysts postulated a psychological basis. In 1893, Sigmund Freud (1856–1939) wrote that the multiple tic disorder was neurotic in nature and that its cause could only be found by delving into the unconscious. In 1921, Hungarian psychiatrist Sándor Ferenczi (1873–1933) referred to tics as 'stereotyped masturbatory equivalents'. Along these lines, in 1948, Eduard Ascher, professor of psychiatry at the Johns Hopkins University, suggested that the complex tics echolalia and coprolalia were 'related to certain attitudes ... toward one or both parents, and also constituted an attempt to suppress their expression'. Under the guidance of psychoanalyst Margaret Mahler (1897–1985), a generation of American psychiatrists learned that the symptoms described by Gilles de la Tourette were signs of a deeper psychosexual disturbance, albeit informed by organic factors. Mahler's clinical case histories led to the

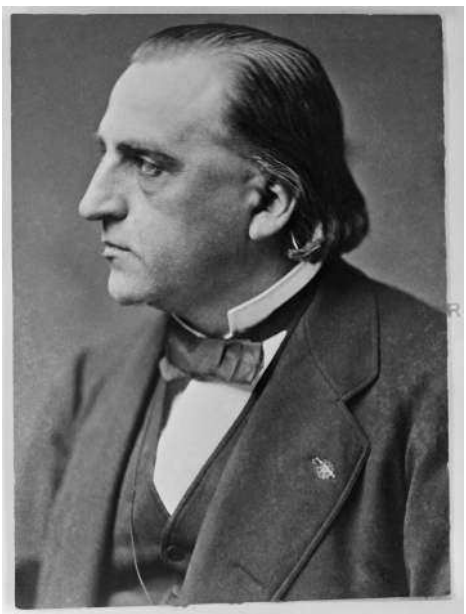

Figure B Jean-Martin Charcot (1825–93).

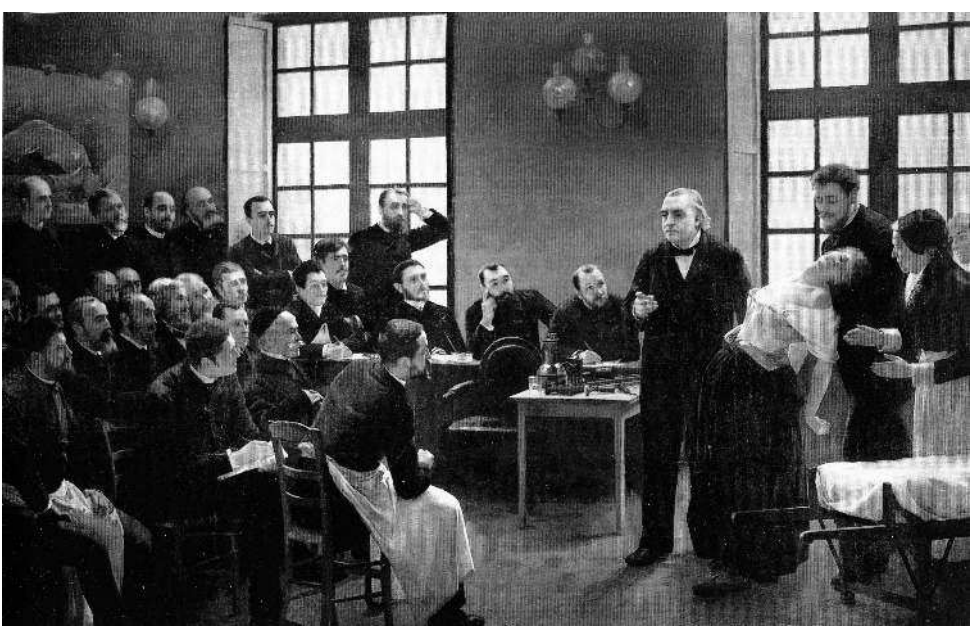

Figure C *Une Leçon Clinique à la Salpêtrière* (A Clinical Lesson at the Salpêtrière), André Brouillet (1887). Charcot is standing next to the patient, and his pupil Gilles de la Tourette is sitting in the front.

conclusion that tic disorders resisted psychoanalytic interventions because the role of the tic was the last 'desperate defense against psychosis'.

Seignot's 1961 scientific report of a case of Tourette syndrome effectively treated with Haloperidol promoted a further 'paradigm shift' from the psychoanalytic theories to the current genetic and neurochemical theories on the aetiology and pathogenesis of Tourette syndrome. Seignot's observation was replicated throughout the world, starting with Caprini and Melotti's case report, which was published in the same year. The introduction of a pharmacological agent to control tics led to the speculation about a neurochemical substrate upon which medications work. Specifically, the unprecedented success of Haloperidol in controlling tics by blocking dopamine receptors in the brain pointed towards a possible excess of dopaminergic neurotransmission. American psychiatrists Arthur and Elaine Shapiro championed the description of Tourette syndrome as a neurological disorder that by definition stood in opposition to psychoanalytic claims. The psychoanalytic perspective was successfully challenged in a book on Tourette syndrome published by the Shapiros in 1978. This paradigm shift in turn kindled interest in tracing the genetic basis of Tourette syndrome, a line of research which has flourished since the 1970s. Throughout the 1980s, studies on other first-generation anti-dopaminergic medications, as well as alpha-2 adrenergic medications, were published, whereas in the 1990s, the second generation of anti-dopaminergic medications were developed. During the first decade of the new millennium, Aripiprazole (sometimes referred to as 'third-generation anti-dopaminergic medication') was first shown to be characterized by good efficacy and tolerability in the treatment of tics. More recently, a range of other medications belonging to different pharmaceutical classes have been investigated in patients with Tourette syndrome. The vast majority of these medications are pharmacological agents initially developed to treat other neuropsychiatric conditions.

In general, the efficiency of medication research and development, measured simply in terms of the number of new drugs brought to market by the global biotechnology and pharmaceutical industries per research and development spending, has declined fairly steadily. This negative trend has been referred to as 'Eroom's Law', in contrast to the more familiar Moore's Law (spelled backwards), the law that describes the exponential increase in the number of transistors that can be placed at a reasonable cost onto an integrated circuit. Figures show that this number doubled every two years from the 1970s to 2010, and the term Moore's Law is now used more generally for technologies that improve exponentially over time. On the contrary, in the US, it has been observed that the number of new Food and Drug Administration–approved medications per billion dollars of research and development spending in the drug industry has halved approximately every 9 years since 1950, in inflation-adjusted terms. The different degree of complexity and limited current understanding of biological systems versus the relative simplicity and higher level of understanding of solid-state physics and information technology explains part of the contrast between Moore's Law and Eroom's Law. It is also possible that Eroom's Law in pharmacology is related to the so-called *better than the Beatles problem* ('imagine how hard it would be to achieve commercial success with new pop songs if any new song had to be better than the Beatles, if the entire Beatles catalogue was available for free, and if people did not get bored with old Beatles records'). It has been suggested that something similar

applies to the discovery and development of new medications, and the pharmacotherapy of Tourette syndrome is no exception to this wider trend.

Rational Pharmacotherapy for Tics

In 2014 the Tourette Association of America described Tim Howard, the former goalkeeper of English Premier League football teams and of the US national soccer team, as 'the most notable person in the world with the condition' and conferred on him their Champion of Hope Award. Interestingly, in his autobiography *The Keeper* (2014) and associated media interviews, Howard stated that he does not take or advocate pharmacotherapy, referring to such treatment as 'a concoction of drugs for other ailments' and suggesting that anti-tic medications 'make you drowsy, make you zombie-like'. Indeed, a 2015 systematic review of the prevalence and management of the adverse effects of anti-dopaminergic drugs, the most commonly used medications for tic control, was titled 'First Do No Harm'. It is widely acknowledged that the adverse effects of anti-dopaminergic medications are diverse and common, albeit not often systematically assessed, with a potential negative impact on adherence and engagement. There is some evidence suggesting that parents of young patients with Tourette syndrome have concerns about adverse effects of medications for tics, especially anti-dopaminergic agents. However, there is also evidence that young patients with Tourette syndrome and parents of young patients with Tourette syndrome can have positive perceptions of anti-tic medication. A large UK-based study published in 2015 explored how these two groups of participants perceive different treatment strategies for tics. In addition to the known concerns and limitations about taking medication for tics (mainly regarding the perceived adverse effects and limited beneficial effects), there were interesting reports on the positive experiences of medication for tics. Specifically, young patients with Tourette syndrome who had taken medication for tics felt that it helped them to reduce their tics or to have better control over them. A considerable proportion of participants reported that medication for tics allowed them to feel less self-conscious about their tics and to disguise them better when in public. A few of the participants who endorsed this theme commented specifically on the dopamine receptor partial agonist Aripiprazole: for example, 'I find Aripiprazole helps quite a lot actually-I am not as bad as I was. I don't have many tics during the day or anything anymore'. Parents also identified that medication could be helpful for the children's tics. Another important theme that emerged from this study is the patients' and parents' concern that health care professionals have limited knowledge of Tourette syndrome, with relevant implications in terms of accessing and receiving evidence-based treatment. These findings are in line with the results of a previous study conducted in Spain, in which young patients with Tourette syndrome and their parents described difficulties receiving a diagnosis of Tourette syndrome that were associated with a lack of knowledge regarding tics among health care professionals. Moreover, since pharmacotherapy is a common treatment for tics, young patients and their families may value receiving clear information regarding the rationale for using medications and their potential adverse effects.

In writing this book, it was the author's goal to fill a gap in the rapidly expanding literature on Tourette syndrome by producing a handy reference manual directed at movement disorders specialists and professionals treating patients with tics, but potentially useful to anyone interested in the pharmacological therapy of tics. This book's practical approach and pocket size should make it a particularly valuable resource for medical practitioners working

in busy clinics with patients with Tourette syndrome and other tic disorders. The text is divided into three parts. Part I covers background information of practical use to diagnose Tourette syndrome and assess tic severity. Specifically, the first chapter focuses on the clinical evaluation and differential diagnosis of tics and related disorders, whereas the second chapter is devoted to the use of psychometric instruments, encompassing recommended rating scales for tic severity, premonitory urges and quality of life. Part II consists of four chapters on the most widely used pharmacological options for tics, grouped according to their mechanisms of action (first- and second-generation anti-dopaminergic medications, alpha-2 adrenergic medications and other tic-suppressing medications). Within each chapter, individual medications are presented in alphabetical order for easier information gathering, thus enabling physicians to use the text as a stand-alone reference in busy clinical settings, such as specialist movement disorders clinics or general neurology ward rounds. Particular care has been taken in covering the key medications used for tic control, detailing for each agent the main pharmacodynamic and pharmacokinetic properties, relevant medicinal forms, titration schedules, indications, contra-indications, tolerability profiles, clinically relevant interactions and recommendations for use in special populations. This information is followed by a summary of the behavioural neurology profile and the recommendations for the use of each medication according to published guidelines on the treatment of tics. Each monograph closes with a section providing a visual overall rating in terms of efficacy for tics and behavioural problems, as well as tolerability of the medication, again drawing on the existing evidence. While the underlying pharmacology is presented to provide a quick refresher and background on the underlying mechanisms, the text has been deliberately focused to cover practical aspects related to the pharmacotherapy of tics following the most up-to-date evidence-based guidance. However, it is important to note that most recommendations on clinical practice in the field of behavioural neurology are empirical, as data based on methodologically sound research are often lacking. Coherence is maintained by the use of a standard template for each medication, with consistency in both required information and writing style. Finally, the existing international guidelines on the pharmacotherapy of tics (based on systematic literature review/meta-analysis and expert consensus) are described in two chapters within Part III.

In line with the practical aims of the book, particular care has been taken in the selection of the references at the end of the volume: a list of primary sources which could serve as first ports of call for readers who are keen to explore in greater depth the clinically relevant information presented in a concise way within each chapter. The vast majority of the referenced work therefore consists in review articles and books published over the past two decades, with a few notable exceptions (Figure D). The presented material was also selected in an attempt to highlight how the behavioural neurology/neuropsychiatry approach could open up privileged avenues to the understanding of the expression of tics and co-morbid behavioural symptoms in patients with Tourette syndrome.

Most of the text is devoted to the illustration of the pharmacotherapy of tics, with only brief mention of other treatment options, such as neurosurgery (deep brain stimulation), which is a more invasive approach still at a pioneering stage, and behavioural interventions, which are more established interventions and would probably deserve more space or a separate book. This is only one of the several shortcomings of the present work, which will not have escaped the attention of more learned readers. Behavioural neurologists and neuropsychiatrists are probably among the best placed readers to appreciate that accuracy and comprehensiveness have often been sacrificed on the altar of simplification and conciseness. It is to them that the author's most sincere apologies should go, in the hope that

Figure D Tourette syndrome: a library.

these are not sacrifices made in vain. Important omissions encompass the treatment of the behavioural co-morbidities of Tourette syndrome, which can affect health-related quality of life to a higher extent than tics. There is, however, mention of the clinically relevant role of anti-dopaminergic medications for tic-related obsessive-compulsive disorder and alpha-2 adrenergic agonists for co-morbid attention-deficit hyperactivity disorder. Moreover, the list of anti-tic medications is far from exhaustive. For example, there are no chapters on the newer and not-yet-established treatments for tics that are currently under investigation, such as the newer anti-dopaminergic medication Ecopipam and cannabinoids. Finally, the information about medication dosages and indications is based on data from adult populations.

After psychoeducation, the first important step in the management of Tourette syndrome is the optimization of treatment interventions in patients presenting with tics and co-morbid behavioural symptoms. The present book aims to be a pocket-sized guide to assist neurologists in the use of pharmacotherapy when treating patients with Tourette syndrome and associated behavioural problems. Psychiatrists treating patients with neurodevelopmental conditions might also find in this volume a useful tool for their clinical practice. It is expected that the prescribing habits of treating clinicians are based on a better understanding of the nature of tics, the characteristics of the patients and the principles of rational pharmacotherapy. Rational pharmacotherapy processes include choosing suitable medications, at an optimum dose and duration of use, among the effective and safe pharmacological options that are available. Providing patients with accurate information about the diagnosis and treatment is equally important in order to optimize the risk-benefit ratio of the chosen medications. The borderlands between neuropharmacology and psychopharmacology chartered in this book

should offer valuable resources to treating clinicians who prioritize health-related quality of life as a therapeutic outcome for their patients. It has been noted that there can be two explanations for the surprisingly low prevalence of persons displaying tics in the street scene: the alleviating effect of medication and the tendency of persons with Tourette syndrome to avoid public spaces. It is the author's hope that this book contributes to make the former explanation more likely than the latter.