Introduction

The year 2018 marked the 60th anniversary of clozapine's synthesis, and the 30th anniversary of the September 1988 *Archives of General Psychiatry* paper by Kane and colleagues documenting clozapine's superior efficacy in treatment-resistant schizophrenia [1]. The peer view literature since 1988 demonstrates ongoing interest in clozapine, with 350–450 papers per year listed in PubMed (see Figure 1). The ensuing decades have also seen other evidence-based uses for clozapine (e.g. schizophrenia patients with suicidality or aggression, Parkinson's disease psychosis, treatment-resistant mania), but treatment-resistant schizophrenia spectrum disorders remain the most common indication. Lamentably, clozapine remains significantly underutilized for treatment-resistant schizophrenia despite compelling evidence of efficacy in this population, and the enormous individual and societal benefits that can accrue from effective management of treatment-resistant patients [2].

To fully appreciate the economic impact of treatment-resistant schizophrenia, one must understand the enormity of the disease burden exacted by schizophrenia. Schizophrenia prevalence remains low, with the global estimate of 0.28% remaining unchanged from 1990 to 2016. The 2016 age distribution of disease also mirrored that in 1990, but the total number of cases rose nearly 60% due to population increases (see Figure 2 and Table 1). There are now close to 21 million persons worldwide with schizophrenia, most of whom require extensive supportive resources. A 2012 meta-analysis indicated that only 13.5% of schizophrenia patients meet criteria for functional recovery; moreover, in addition to lengthy periods of disability, schizophrenia patients suffer premature mortality due to natural and unnatural causes [3]. The World Health Organization (WHO) quantifies the dual impact of disorders using the outcome of disability-adjusted life year, a measure that sums the years lived with disability and those lost due to early mortality. Schizophrenia ranked twelfth overall among 310 conditions (i.e. diseases or injuries) studied in the WHO Global Burden of Disease Study 2016, and acute schizophrenia carried the highest disability weight

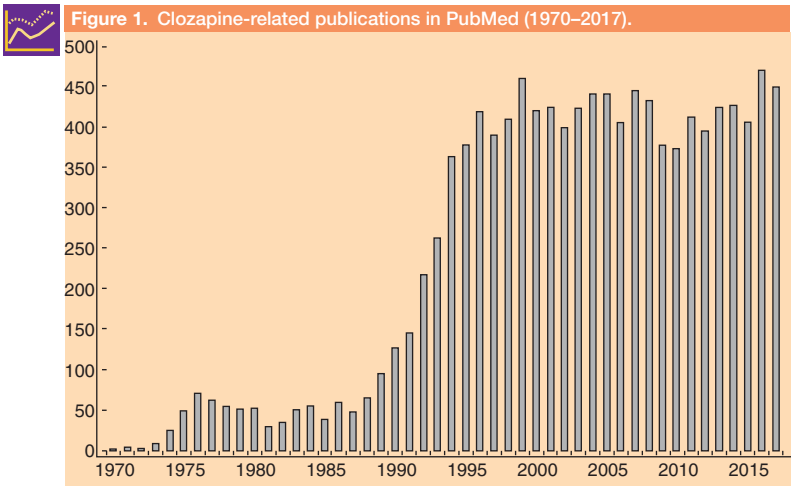


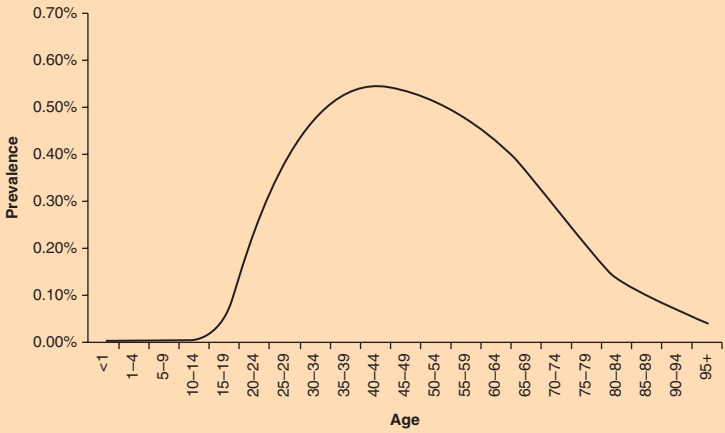
Figure 1. Clozapine-related publications in PubMed (1970–2017).

among all disorders [3,4]. Despite its low global prevalence of 0.28%, schizophrenia contributed 13.4 million years of life lost due to disability in 2016. This represented 1.7% of the total in the 2016 WHO study, a value sixfold greater than the prevalence of schizophrenia. For the United States (US) alone, the combination of direct health care costs, direct nonhealth-care costs (law enforcement, homeless shelters, health-care 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 health-care costs (24%).

Treatment-resistant schizophrenia patients are but a fraction of the schizophrenia population, yet they exert an outsized influence on the costs associated with this disorder. While there is active debate about the definition of treatment resistance for clinical and research purposes, an estimated 20–30% of schizophrenia patients fail to adequately respond to two or more documented antipsychotic trials of sufficient dosage and duration [6,7]. A 2014 review on the social and economic burden of treatment-resistant schizophrenia found 65 papers published from 1996 to 2012 to provide data for relative cost estimates [6]. Based on this extensive literature review, annual costs for patients with schizophrenia in the US were three- to 11-fold higher

for those who were treatment-resistant, with hospitalization costs and total health-resource utilization 10-fold higher among this cohort than for schizophrenia patients in general (see Figure 3). The authors concluded that treatment-resistant schizophrenia

Figure 2. Mean schizophrenia prevalence by age in 2016.



(Adapted from: Charlson, F. J., Ferrari, A. J., Santomauro, D. F., et al. (2018). Global epidemiology and burden of schizophrenia: findings from the Global Burden of Disease Study 2016. *Schizophrenia Bulletin* 44, 1195–1203.)

Table 1 Age-standardized schizophrenia prevalence in 1990 and 2016 [3].

Region	Total number of cases (in 1000s)		Prevalence (%)	
	1990	2016	1990	2016
Southeast Asia, East Asia, and Oceania	5869.3	9109.4	0.38	0.38
Central Europe, Eastern Europe, and Central Asia	865.9	987.0	0.20	0.21
South Asia	2112.1	3986.1	0.25	0.25
Australasia	71.5	105.9	0.33	0.33
Western Europe	1029.4	1242.9	0.24	0.25
High-income North America	884.6	1214.7	0.30	0.30
Latin America and Caribbean	635.0	1186.5	0.20	0.20
North Africa and Middle East	443.9	1014.7	0.18	0.19
Sub-Saharan Africa	619.0	1314.1	0.19	0.19
Global	13,122.1	20,883.0	0.28	0.28

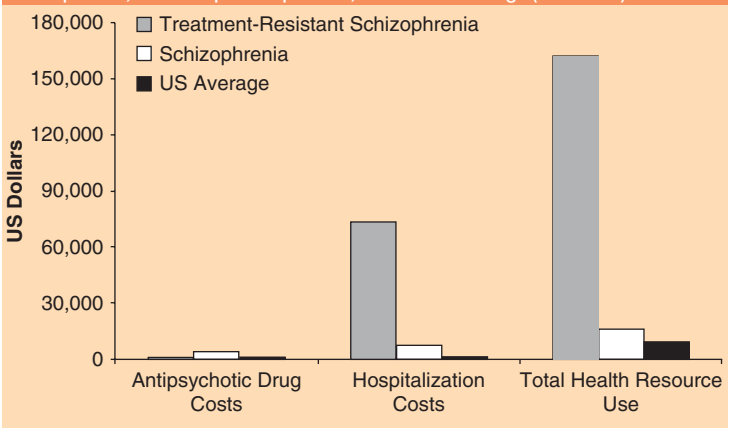


Figure 3. Health-care costs per patient-year for US patients with treatment-resistant schizophrenia, all schizophrenia patients, and the US average (2012 USD).

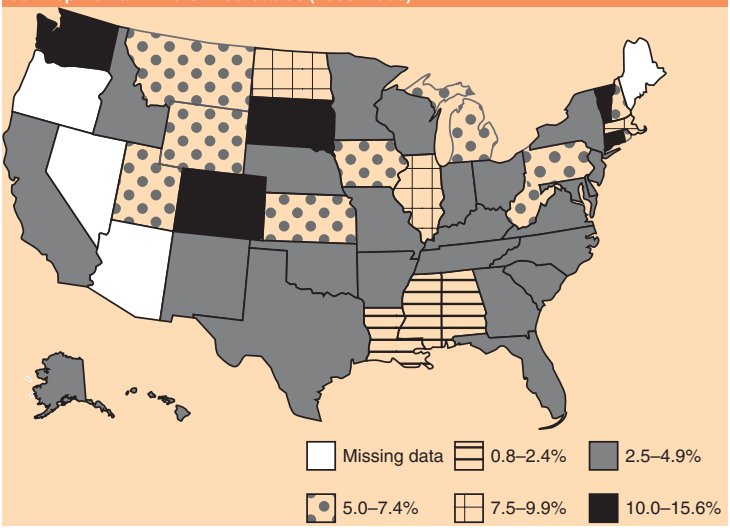
(Adapted from: Kennedy, J. L., Altar, C. A., Taylor, D. L., et al. (2014). The social and economic burden of treatment-resistant schizophrenia: a systematic literature review. *International Clinical Psychopharmacology*, 29, 63–76 [6].)

conservatively adds more than $34 billion in annual direct medical costs in the US [6]. On a personal level, quality of life for schizophrenia patients who are unresponsive or intolerant to treatment is 20% lower than that of patients who achieve more robust symptomatic improvement [6].

Clinicians are often more focused on alleviating individual suffering than the societal impact of disease burden, but despite widespread availability and compelling efficacy data clozapine remains underutilized for treatment-resistant schizophrenia [2]. Although 20–30% of schizophrenia patients are treatment-resistant, only six of 50 states in the US report that more than 10% of schizophrenia patients have received a prescription for clozapine; moreover, many clozapine candidates are subjected to years of multiple, ineffective antipsychotic trials. Systemic issues are one disincentive to clozapine use for outpatients, with one workgroup noting that most mental health-care systems lack "a centralized infrastructure for coordinating the array of services required by persons receiving clozapine" [2]. While one might assume that more densely populated urban areas would have the resources to support new clozapine

treatment, a 2014 analysis of US clozapine prescribing in 2002–2005 noted that, on a county level, there was no significant effect of population density or measures of poverty or income on clozapine initiation, though a higher density of psychiatrists (≥ 15 per 100,000 population) was associated with a greater likelihood of commencing clozapine [8]. Certain factors, such as age, gender, race, substance use and medical comorbidity all played roles in clozapine usage, but geographic location emerged as a significant overriding predictor, suggesting that local culture in certain areas reinforces evidence-based practice, while that in other areas tolerates the notion that "We don't prescribe clozapine in this area" as an acceptable response to managing treatment-resistant schizophrenia (see Figure 4). Bolstering this argument are data from that 2014 analysis which indicate that patients residing in US counties that had historically

Figure 4. Clozapine prescribing rates among publicly insured adults with schizophrenia in the United States (2006–2009).



(Adapted from: Olfson, M., Gerhard, T., Crystal, S., et al. (2016). Clozapine for schizophrenia: state variation in evidence-based practice. *Psychiatric Services*, 67, 152 [16].)

high clozapine usage were nearly twice as likely to start clozapine as patients residing in historically low-use counties [8]. This problem is not unique to the US, as 2002 prescribing data from the United Kingdom (UK) found a 34-fold variation in clozapine use across National Health Service (NHS) trusts [9]. One practical obstacle to clozapine treatment among patients of African descent has been benign ethnic neutropenia (BEN), but revisions of absolute neutrophil count (ANC) thresholds for BEN individuals in many countries has markedly reduced the impact of this benign variant [10].

PRESCRIBER FEAR

While recent US changes to ANC thresholds for all patients (including new BEN thresholds) have enlarged the pool of individuals who can start clozapine, there is one barrier that no regulatory authority can overcome, and that is clinician fear of prescribing clozapine [10,11]. Despite the overwhelming evidence that patients on clozapine have lower mortality from natural and unnatural causes, enhanced quality of life due to reduced symptom burden, and that no other antipsychotic is robustly effective for treatment-resistant schizophrenia, numerous papers document overestimation of safety concerns combined at times with a misunderstanding of the tremendous efficacy difference between clozapine and other antipsychotics for treatment-resistant schizophrenia. In an article entitled "Prescribers Fear as a Major Side-Effect of Clozapine", Professor Dan Cohen (Mental Health Organization North-Holland North, Heerhugowaard, The Netherlands) comments:

> This unscientific and irrational fear is a clinically relevant phenomenon as it causes psychiatrists to withhold their patients an effective, evidence-based treatment, thereby unnecessarily prolonging their patients' suffering. [11]

The net result is that many psychiatrists either refuse to prescribe clozapine, or do so in a limited manner, a finding seen in studies across the globe including the US, Denmark, India and the UK [12–15]. Given the enormous social and economic impact of clozapine use, large health-care systems have taken note of this gap between evidence-based practice and the routine underuse of clozapine for treatment-resistant schizophrenia, and have commenced initiatives to promote clozapine prescribing. In the UK, variation in clozapine use across NHS trusts was reduced from 34-fold in 2002 to 5-fold by 2006 in part due to the publication of national guidelines recommending clozapine after inadequate response to two antipsychotics [9]. In other places, more intensive, coordinated efforts have been devised employing some or all of the principles outlined in Box 1.

Box 1 Strategies for Increasing Clozapine Utilization [11,15]

1. Establishment of national or regional (e.g. state-wide) clozapine expertise centers tasked with performing three essential functions:
   - **a.** Real-time consultation without a fee on treatment indications, clozapine initiation, drug–drug interactions, prevention or management of adverse effects.
   - **b.** Provide educational outreach to mental health professionals through lectures, publications, and written summaries of important clinical points (e.g. constipation management).
   - **c.** Modernizing local clozapine prescribing guidelines (as recently performed in the US) to reduce initiation and treatment burdens, remove unnecessary monitoring requirements (e.g. total white blood cell count), lower absolute neutrophil count (ANC) thresholds for all patients, establish appropriate lower ANC thresholds for those with benign ethnic neutropenia, and other evidence-based changes as indicated by developments in the literature.
2. Development of a national or regional (e.g. state-wide) pharmacy surveillance system to identify all schizophrenia patients that are prescribed a third antipsychotic other than clozapine. When this occurs, the prescriber must provide documentation justifying this choice in lieu of clozapine. Such documentation must include the fact that the patient has been informed of the specific benefits of clozapine (e.g. symptom reduction, mortality reduction, lower suicide rate), and include the patient's signature (and that of a caregiver or guardian if the patient lacks capacity) noting the date of the discussion.
3. Incentivizing clinic systems to promote clozapine prescribing through financial methods (e.g. money for training or technical assistance).
4. Publication of regional clozapine usage rates for clinic systems (per 100 schizophrenia spectrum patients) on an annual basis to clearly identify persistent areas of underutilization. Detailed action plans will be demanded from centers with low levels of clozapine use.
5. Creation of internet-based education programs geared towards consumers and family members. One model is the New York State Office of Mental Health web-based module "Considering Clozapine" that provides information about clozapine (including benefits and risks), and includes a series of testimonials from consumers who describe personal benefits from clozapine along with its challenges.

Elements of these programs include support and education of clinicians to enhance their ability to manage clozapine-treated patients, and ongoing system-wide surveillance of clozapine usage rates to reinforce the new cultural norm that underuse of clozapine is a mark of substandard psychiatric practice. The engendered fear of

using clozapine is often simply a byproduct of inadequate education and not clinician indifference to the patient's condition, but providing information to clinicians, patients and families about clozapine's benefits is not enough. The creation of a clozapine resource center was an important aspect of programs established in the Netherlands and in New York State. These centers were typically staffed by knowledgeable senior psychiatrists and thereby allowed clinicians immediate answers to pressing questions during working hours. The value of the personal connection and the immediacy of the response cannot be underestimated. In the Netherlands prescriptions for all antipsychotics rose 8.2% from 2008 and 2012, but through the efforts of the Dutch Clozapine Collaboration Group (www.clozapinepluswerkgroep.nl) clozapine use in this same interval rose by 20% [11]. Across the state of New York the proportion of new clozapine starts increased by 40% from 2009 to 2013 following commencement of their "Best Practices Initiative – Clozapine" in 2010 [15]. Importantly, the quarterly percentage change in rate of clozapine initiation among state run facilities was threefold higher than in other settings, illustrating the concept that local changes in culture with respect to clozapine prescribing are self-reinforcing. As more clinicians in a practice setting develop comfort with and expertise in clozapine prescribing, those who fail to meet the new expectations of competence will increasingly be viewed in a negative light by their colleagues.

CONCLUSIONS

There is a worldwide effort to increase clozapine use, but many clinicians lack access to expert consultation services or other centralized resources of information about clozapine. It is hoped that this volume will serve as a unified guide for those clinicians who strive to provide optimal, evidence-based care for their patients in need of clozapine. The focus of this handbook is on the practical management of clozapine initiation and adverse effects, with the idea that each chapter will present a self-contained discussion of a particular topic for the busy clinician. As the reader will discover, there is a paucity of double-blind, placebo-controlled trials governing most aspects of clozapine side-effect management, but patients must be treated with the best tools available, and this handbook uses the extant literature to guide clinicians through various options. The net goal is to demystify the use of clozapine, and empower mental health providers everywhere to provide their patients with this effective, and at times life-saving, medication.

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1 The Efficacy Story: Treatment-Resistant Schizophrenia, Psychogenic Polydipsia, Treatment-Intolerant Schizophrenia, Suicidality, Violence, Mania and Parkinson's Disease Psychosis

QUICK CHECK

INTRODUCTION

The 60th anniversary of clozapine's synthesis by Schmutz and Eichenberger at Wander Pharmaceuticals was celebrated in 2018, although the chemists involved hoped that their tricyclic compound HF-1854 would possess antidepressant effects [1]. In January 1961, the first pharmacological report on HF-1854 described an agent with sedative and antiadrenergic properties that resembled chlorpromazine, but which did not induce catalepsy [1]. Further animal testing reported in December 1961 established a range of activities comparable to chlorpromazine but without the catalepsy induction seen with haloperidol. In 1962 the first open clinical trial of HF-1854 found limited efficacy at the dose of 160 mg TID ($n = 19$), but later that year Gross and Langer in Vienna found good results in 21 of 28 patients at similar dosing, again without neurological adverse effects [2]. Further trial reports to Wander