



Review

Schizophrenia, “Just the Facts” 5. Treatment and prevention Past, present, and future

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ARTICLE INFO

Article history:

Received 5 March 2010

Received in revised form 22 May 2010

Accepted 25 May 2010

Available online 23 July 2010

Keywords:

Schizophrenia

Treatment

Prevention

Pharmacology

Therapy

Antipsychotics

Psychological treatments

Social treatments

Dimensions

Treatment targets

ABSTRACT

The introduction of second-generation antipsychotics and cognitive therapies for schizophrenia over the past two decades generated considerable optimism about possibilities for recovery. To what extent have these developments resulted in better outcomes for affected individuals? What is the current state of our science and how might we address the many unmet needs in the prevention and treatment of schizophrenia? We trace the evolution of various treatments for schizophrenia and summarize current knowledge about available pharmacological and psychosocial treatments. We consider the widely prevalent efficacy–effectiveness gap in the application of available treatments and note the significant variability in individual treatment response and outcome. We outline an individualized treatment approach which emphasizes careful monitoring and collaborative decision-making in the context of ongoing benefit–risk assessment. We note that the evolution of both pharmacological and psychosocial treatments thus far has been based principally on serendipity and intuition. In view of our improved understanding of the etiology and pathophysiology of schizophrenia, there is an opportunity to develop prevention strategies and treatments based on this enhanced knowledge. In this context, we discuss potential psychopathological treatment targets and enumerate current pharmacological and psychosocial development efforts directed at them. Considering the stages of schizophrenic illness, we review approaches to prevent progression from the pre-symptomatic high-risk to the prodrome to the initial psychotic phase to chronicity. In view of the heterogeneity of risk factors, we summarize approaches towards targeted prevention. We evaluate the potential contribution of pharmacogenomics and other biological markers in optimizing individual treatment and outcome in the future.

Published by Elsevier B.V.

1. Introduction

Two decades ago, knowledge about the treatment of schizophrenia was summarized as “antipsychotics are useful in the treatment of schizophrenia and block dopamine receptors in proportion to their relative clinical potency”, and “crisis-oriented family therapy along with antipsychotic medication reduces the risk of psychotic relapses” (Wyatt

et al., 1988). In taking stock of our current body of knowledge (Table 1), we venture to say that day-to-day management of schizophrenia appears not to have changed very much. This is despite the supposed revolutionization of treatment by the introduction of second-generation antipsychotic agents and a range of cognitive psychotherapeutic approaches over this period of time (Pilling et al., 2002a,b; Kane et al., 2003; Falkai et al., 2005). In an effort to explore this discrepancy, we first summarize our current knowledge about pharmacological, psychological, social, and other emerging treatments for schizophrenia. We next evaluate challenges in bridging the

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Table 1

Fact	Reproducibility	Specificity to illness	Durability of finding over time
<i>Prevention and treatment [reducing morbidity and mortality]</i>			
Dopamine-2 antagonists (“antipsychotics”) are the only effective therapeutic agents which are currently available.	***	*	***
Antipsychotic agents are most effective for positive symptoms.	**	*	**
Clozapine is more effective than other agents for neuroleptic-refractory positive symptoms and suicidality.	**	*	**
No major differences in efficacy across patients between other currently available antipsychotic agents are consistently noted.	**	*	**
Antipsychotics have limited efficacy on negative symptoms and cognitive deficits.	**	**	**
Extrapyramidal side-effects are not necessary for an antipsychotic effect and compromise benefit on cognitive, negative, and mood symptoms.	**	—	**
Antipsychotics vary widely in their adverse effect profiles.	***	—	***
Antidepressants are effective in treating depressive symptoms.	**	—	**
Electroconvulsive therapy may be effective.	*	*	***
Transcranial magnetic stimulation (rTMS) can be effective.	*	*	*
Family and patient psychoeducation reduce relapse rates.	**	*	**
Cognitive behavior therapy reduces psychotic symptoms.	**	*	*
Social skills training improves outcomes.	**	*	**
Assertive community treatment reduces hospitalization rates.	**	*	**
Cognitive remediation reduces cognitive deficits.	*	*	*
Early intervention in high-risk individuals with pharmacological and psychosocial treatments prevents development of schizophrenia.	*	*	*
Early intervention during first episode of psychosis improves outcomes.	**	*	**

Reproducibility: *:few or inconsistent replications; **:well replicated with a few failures to replicate; ***:many and consistent replications.

Specificity to illness: -:not specific; *:some specificity but found in other conditions; **:moderate specificity; ***:high specificity.

Durability of finding: *:new finding over past decade; **:finding noted over past 10–20 years; ***:finding noted for over 20 years.

science-to-service gap in schizophrenia treatment and suggest approaches to implement evidence-based individualized treatment. Looking to the future, we note that a sea-change of developments has occurred in the conceptualization of schizophrenia setting the stage for significant future therapeutic innovations. We review how such developments might reshape our approach to better defining treatment targets and developing more efficacious and potentially illness-modifying therapies.

Our objective is to provide a succinct critical appraisal of existing treatments for schizophrenia, note gaps in knowledge and limitations of current treatment approaches, and outline strategies to address the several unmet needs. Our approach was described in the first article in this series (Tandon et al., 2008a).

2. Pharmacologic treatments

Schizophrenia is a chronic remitting and relapsing disorder associated with shortened lifespan and significant impairments in social and vocational functioning. Comprehensive treatment entails a multi-modal approach, including medication, psychosocial interventions, and assistance with housing and financial sustenance. The broad objectives of treatment are to reduce the mortality and morbidity of the disorder by decreasing the frequency and severity of episodes of psychotic exacerbation and improving the functional capacity and quality of lives of the individuals afflicted with the illness. When Emil Kraepelin (1919) first described the concept of schizophrenia a century ago (Fig. 1), he asserted “the treatment of dementia praecox offers few points of intervention”. Until the introduction of antipsychotics into clinical practice 50 years later, standard treatment for schizophrenia consisted of providing patients with a safe and supportive environment in the form of a long-stay

psychiatric hospital and hoping for the elusive spontaneous remission. Although electroconvulsive therapy was occasionally utilized as were subsequently discredited ‘treatments’ such as insulin coma therapy and prefrontal leucotomy (Sakel, 1937; Swayze, 1995), care was primarily custodial until the 1950s. The introduction of the first antipsychotic chlorpromazine into clinical practice a half-century ago sparked the revolution in the pharmacotherapy of schizophrenia (Delay et al., 1952). Antipsychotic medications became the cornerstone in the pharmacological treatment of schizophrenia and three of these agents (chlorpromazine, fluphenazine, and haloperidol) are included in the World Health Organization’s list of Essential Medications (World Health Organization, 2009). Over 60 antipsychotic medications have been developed and they are classified into groups of first- and second-generation agents, Table 2). The one pharmacological property shared by all currently available antipsychotic agents is their ability to block the dopamine D-2 receptor (Johnstone et al., 1978; Kapur and Remington, 2001), with their clinical antipsychotic potency found to correlate with their affinity for the receptor (Creese et al., 1976; Seeman et al., 1976).

2.1. Comparative effectiveness of antipsychotics in the treatment of schizophrenia

First-generation antipsychotic agents (FGAs) are fairly effective in reducing positive symptoms of the disorder (hallucinations and delusions) in a large proportion of patients and enabled the deinstitutionalization of persons with schizophrenia in the 1960s. These medications are, however, minimally effective against negative and cognitive symptom domains which contribute too much of the illness-related disability (Wyatt et al, 1988; Tandon et al., 2009). Additionally, FGAs cause a range of treatment burdens

Psychological and Social Treatments

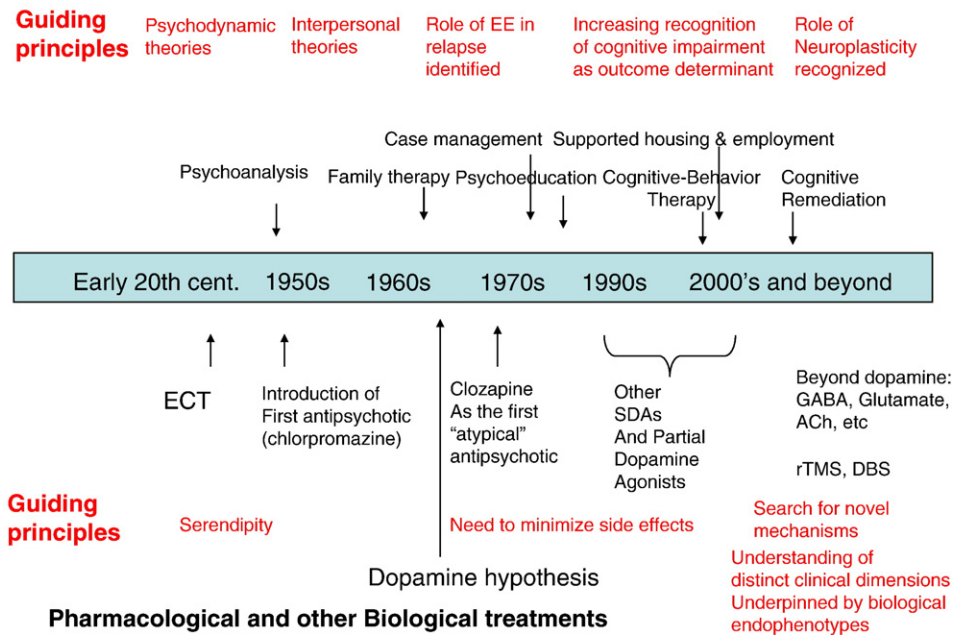


Fig. 1. Evolution of treatments for schizophrenia.

including acute extrapyramidal symptoms and tardive dyskinesia (Nasrallah and Tandon, 2009).

Clozapine, the first so-called atypical or subsequently labeled "second-generation" antipsychotic (SGA), was introduced into clinical practice in the late 1960s. It does not cause EPS or tardive dyskinesia. Its other adverse effects, however, have substantially limited its utilization and agranulocytosis kept it out of most parts of the world until the 1990s (Crilly, 2007). The fact that it was found to be more effective than FGAs in treatment-refractory patients (Kane et al., 1988) and in reducing suicidality (Meltzer et al., 2003), and was devoid of significant short-term and long-term motor side-effects led to optimism that better antipsychotic treatments for schizophrenia were possible. Substantial efforts to develop "a safer clozapine" have led to the introduction of twelve additional SGAs (Table 2) into clinical practice over the past fifteen years (Fig. 1). Initially believed to be more efficacious and tolerable than the 51 first-generation neuroleptics, these thirteen "atypical" or second-generation antipsychotics have progressively displaced the older agents in the treatment of schizophrenia and have become the standard of care. Results of recent large-scale studies comparing the effectiveness of FGAs versus SGAs in schizophrenia, however, appear to indicate that SGAs are no more effective than FGAs and are not associated with better cognitive or social outcomes (Lieberman et al., 2005; Jones et al., 2006; Keefe et al., 2007; Swartz et al., 2007). Recent data among first-episode and early-onset schizophrenia patients also suggest the absence of significant benefits of SGAs over FGAs (Kahn et al., 2008; Sikich et al., 2008; Davidson et al., 2009b).

How effective are antipsychotics in the treatment of schizophrenia and how do different agents compare?

2.2. Efficacy

Antipsychotic medications are consistently superior to placebo in reducing overall symptoms and risk of relapse in patients with schizophrenia (Cole, 1964; Gilbert et al., 1995; Leucht et al., 2003; Adams et al., 2009). The effect sizes for efficacy across various symptom domains are moderate (Table 3). No major differences in efficacy across various antipsychotic agents have been observed in meta-analyses of placebo-controlled studies (Leucht et al., 1999; Srisurapanont and Maneeton, 1999; Leucht et al., 2009a), with haloperidol found to have similar efficacy to the various SGAs. In contrast to the absence of differential efficacy noted in placebo-controlled trials, meta-analyses of haloperidol-controlled trials indicate that some SGAs (notably clozapine, olanzapine, amisulpride, and risperidone) but not the others are more effective than haloperidol (Davis et al., 2003; Leucht et al., 2009b). This observation has, in part, been explained as a methodological artifact of differences in the comparator dose of haloperidol employed in the different trials (Geddes et al., 2000; Tandon and Nasrallah, 2006; Hugenholtz et al., 2006). Comparisons of SGAs against low- and mid-potency FGAs are limited but suggest the absence of consistent differences in FGA-SGA efficacy except for the superiority of clozapine in treatment-refractory schizophrenia (Kane et al., 1988; Bonham and Abbott, 2008). Similarly, direct comparisons among low-, mid-, and high-potency FGAs are limited but suggest the absence of consistent differences in efficacy (Casey et al., 1960; Cole, 1964; Hollister, 1974; Davis et al., 1980). Finally, direct comparisons between different SGAs reveal inconsistent differences in acute efficacy (Johnsen and Jorgensen, 2008; Tandon et al., 2008c; Leucht et al., 2009c) but indicate an advantage in efficacy for clozapine over other SGAs in

Table 2

List of first- and second-generation antipsychotics.

First-generation antipsychotics (N = 51)	
I. Phenothiazines	
(A) Aliphatic side chain	Chlorpromazine, chlorproethazine, cyamemazine, levomepromazine, promazine, triflupromazine.
(B) Piperidine side chain	Mesoridazine, piperacetazine, pipotiazine, propericiazine, sulforidazine, thioridazine.
(C) Piperazine side chain	Fluphenazine, acetophenazine, butaperazine, dixyrazine, perazine, perphenazine, prochlorperazine, thiopropazate, thioproperazine, trifluoperazine
II. Butyrophenones	Haloperidol, benperidol, blonanserin, bromperidol, droperidol, fluanisone, melperone, moperone, pipamperone, timiperone, trifluoperidol.
III. Thioxanthenes	Thiothixene, chlorprothixene, clopenthixol, flupenthixol, zuclopenthixol
IV. Dihydroindolones	Molindone, oxypertine
V. Dibenzoxazepines	Loxapine, clotiapine
VI. Diphenylbutylpiperidines	Pimozide, fluspirilene, penfluridol
VII. Benzamides	Sulpiride, nemonapride, sultopride, tiapride
VIII. Iminodibenzyl	Clocapramine, mosapramine
Second-generation antipsychotics (N = 13)	
I. Benzo (diaz- or thiaze-) pines	Asenapine, Clozapine, Olanzapine, Quetiapine, Zotepine
II. Indolones and diones	Aripiprazole, iloperidone, paliperidone, perospirone, risperidone, \sertindole, ziprasidone
III. Benzamide	Amisulpride

treatment-refractory schizophrenia (Wahlbeck et al., 1999; Chakos et al., 2001; Lewis et al., 2006; McEvoy et al., 2006) and greater treatment persistence for olanzapine over other agents in chronic schizophrenia (Lieberman et al., 2005; Johnsen and Jorgensen, 2008; Leucht et al., 2009c). Comparative studies in the early stages of schizophrenic illness portray a similar profile and indicate the absence of significant differences in efficacy among different antipsychotic agents

(Armenteros and Davies, 2006; Kahn et al., 2008; Sikich et al., 2008; Salimi et al., 2009; Crossley et al., 2010).

With reference to individual symptom domains (Tandon et al., 2009), all antipsychotic drugs have robust efficacy mainly against positive and disorganization symptom domains (Mazure et al., 1992; Leucht et al., 2009a). There are no consistent differences in efficacy across different agents, with their shared pharmacological property of blocking the dopamine D-2 receptor linked to their efficacy against these symptom domains (Creese et al., 1976; Seeman et al., 1976; Johnstone et al., 1978; Kapur and Remington, 2001). The previously-held belief that extrapyramidal side-effects (EPS) are an unavoidable accompaniment of an antipsychotic effect (Haase and Janssen, 1965) has been discredited (Kapur et al., 2000). Both direct blockade of the dopamine D-2 receptor and secondary depolarization blockade appear relevant to antipsychotic action (Grace et al., 1997; Kapur et al., 2005) as reflected in their onset of action within a few days and achievement of much of their antipsychotic effect over several weeks (Agid et al., 2003; Leucht et al., 2005; Emsley et al., 2006; Sherwood et al., 2006; Jager et al., 2010). Response over the first 2–4 weeks of antipsychotic therapy is highly predictive of long-term response (Lambert et al., 2010; Derks et al., 2010; Kinon et al., 2010). The maximal antipsychotic effect may not be achieved for several months, however, and there is considerable variability in the trajectories of antipsychotic response across patients (Garver, 2006; Levine and Rabinowitz, 2010).

Antipsychotics are less consistently effective in reducing negative symptoms, with much of this effect coupled to reduction in positive symptoms (Breier et al., 1991; Tandon et al., 1993a,b). Whereas antipsychotics ameliorate negative symptoms linked with positive symptoms, they can worsen negative symptoms associated with extrapyramidal side-effects (Carpenter et al., 1988; Stahl and Buckley, 2007). Consequently, their net effect on negative symptoms is determined by the extents to which they reduce positive symptom-associated negative symptoms while triggering EPS-related negative symptoms. Antipsychotic agents have no demonstrable efficacy against primary enduring or “deficit” negative symptoms (Kirkpatrick et al., 2006). Similar to their effect on negative symptoms, antipsychotics ameliorate depressive symptoms in conjunction with improvement in positive symptoms, but can cause “neuroleptic dysphoria” associated with EPS (Voruganti and Awad, 2004). Although

Table 3

Efficacy of antipsychotic treatment in schizophrenia: effect sizes versus placebo.

Psychopathological domain	Most commonly reported outcome variable	Effect size	References
Overall efficacy	PANSS and BPRS	.43–.58 (Hedge's g)	Leucht et al., 2009a
Non-response	Percent Reduction in PANSS or BPRS score or CGI-Improvement	.73–.83 Relative risk .14–.22 Risk difference	Leucht et al., 2009a
Positive symptoms	BPRS and PANSS	.36–.82 (Hedge's g)	Leucht et al., 2009a
Negative symptoms	BPRS and PANSS	.33–.45 (Hedge's g)	Leucht et al., 2009a
Depressive symptoms	BPRS and PANSS	.15–.38 (Hedge's g)	Leucht et al., 2009a
1-year relapse risk	Hospitalization for psychopathology or worsening of scores on BPRS or PANSS	.08–.34 Risk difference [Raw] with NNT = 3–13 .11–.55 Risk difference [Survival curve] with NNT = 2–9	Leucht et al., 2003 Gilbert et al., 1995

antipsychotic medications improve attention in patients with schizophrenia (Harvey and Keefe, 2001; Mishara and Goldberg, 2004), their effects on other cognitive impairments are inconsistent (Mortimer, 1997), may be attributed to a practice effect (Goldberg et al., 2007), and may include worsening (Bilder, 1997; Green and Braff, 2001). There do not appear to be consistent differences between various antipsychotic agents with reference to their effects on neuro-cognitive dysfunction (Keefe et al., 2007; Davidson et al., 2009b; Hill et al., 2010), with their net impact on cognition determined by their beneficial effects on attention and deleterious effects related to EPS and anticholinergic activity.

Antipsychotic medications substantially decrease the likelihood of relapse in patients with schizophrenia (Davis et al., 1976; Gilbert et al., 1995; Leucht et al., 2003; Alkhateeb et al., 2007), without any consistent differences documented among agents. Since medication non-adherence during treatment of schizophrenia is common, long-acting injectable antipsychotic regimens have been found to be variably advantageous over oral antipsychotic treatment approaches in reducing rates of relapse (Hogarty et al., 1986; Adams et al., 2001; Nasrallah, 2007).

Antipsychotic treatment responsiveness varies as a function of illness stage, with first-episode patients responding faster and at a higher rate than those at later stages of the illness (Lieberman et al., 1993; Robinson et al., 1999; Salimi et al., 2009).

2.3. Safety and tolerability

Antipsychotic medications cause a range of neurological, metabolic, cardiovascular, gastrointestinal, hematological, genito-urinary, musculoskeletal, endocrine, and other side-effects. In contrast to their broadly similar efficacy, antipsychotic agents clearly differ in their propensity to cause these adverse effects (Arnt and Skarsfeldt, 1998; De Hert et al., 2009; Stahl et al., 2008; Ciranni et al., 2009; Ozbilen and Adams, 2009; Ray et al., 2009). In comparison to the 51 first-generation antipsychotic medications (FGAs), the class of 13 second-generation agents (SGAs) is believed to be associated with a lower risk of EPS but a higher risk of metabolic adverse effects (Allison et al., 1999; Meyer and Koro, 2004; Miyamoto et al., 2005; Kane, 2006; Crossley et al., 2010). There is substantial variation within both classes of antipsychotic medications with regard to their likelihood to cause EPS and metabolic adverse effects, however, and there is no categorical distinction between so-called FGAs and SGAs with regard to these risks (Newcomer and Haupt, 2006; Weiden, 2007; Yang et al., 2007; Chen and Tandon, 2009; De Hert et al., 2009). The 64 antipsychotic medications differ in their propensity to cause other side-effects such as sedation, hypotension, cardiac arrhythmias, prolactin elevation and related sexual dysfunction, as well as central and peripheral anticholinergic side-effects. There is variation within both the FGA and SGA classes with reference to each of these adverse effects, without any categorical separation between these two classes (Coulter et al., 2001; Glassman and Bigger, 2001; Haddad and Wieck, 2004; Stubner et al., 2004; Smith et al., 2008; Ciranni et al., 2009; Leucht et al., 2009b; Ozbilen and Adams, 2009; Ray et al., 2009).

2.4. Impact on overall outcome

Untreated schizophrenic illness is associated with doubling of age-standardized mortality, poor vocational and social functioning, and impairments in subjective and objective measures of quality of life (Folsom et al., 2005; Eack and Newhill, 2007; Kooyman et al., 2007; Tandon et al., 2009). Although antipsychotic treatment ameliorates a range of symptom domains and reduces likelihood of relapse in patients with schizophrenia, the extent to which such treatment improves lifespan and psychosocial function in patients with schizophrenia is less clear (Lehman et al., 2004).

Despite the use of first- and second-generation antipsychotics, the mortality gap has increased for patients with schizophrenia over the past two decades (Colton and Manderscheid, 2006; Saha et al., 2007). Recent studies on the impact of antipsychotic treatment on mortality in schizophrenia have yielded mixed results (Ren et al., 2009; Tiihonen et al., 2009a; Weinmann et al., 2009). Whereas Ren et al. (2009) observed no differences in mortality between treated and never-treated schizophrenia, Weinmann et al. (2009) observed that long-term exposure to antipsychotics was associated with higher mortality (which they attributed not to antipsychotic treatment but the confound of greater medical comorbidity linked to illness severity). On the other hand, Tiihonen et al. (2009a,b) observed a lower mortality associated with long-term antipsychotic use. They further noted different mortality rates in conjunction with different antipsychotic agents and clozapine stood out as being associated with substantially lower mortality than other antipsychotics. Given clozapine's greater risk of causing many adverse effects expected to increase mortality risk (e.g., agranulocytosis, seizures, and metabolic syndrome), this finding is puzzling; it was explained by the authors as being related to the benefits of better symptom control and treatment adherence with clozapine treatment (Tiihonen et al., 2006). Methodological limitations of the study (de Hert et al., 2010) warrant cautious application of this study's results.

Similarly, the impact of antipsychotic treatment on measures of social function and quality of life in patients with schizophrenia has not been well defined (Wyatt, 1991; DeQuardo and Tandon, 1998). Although some beneficial effects on employment and reducing disability are reported (Eack and Newhill, 2007; Thirthalli et al., 2008, 2010), such effects are inconsistent and modest at best (Lehman et al., 2004; Marwaha and Johnson, 2004; Waghorn et al., 2004). Antipsychotic treatment reduces the likelihood of suicide in patients with schizophrenia with clozapine having the most robust effect (Meltzer et al., 2003).

Our incomplete understanding of the impact of different antipsychotic treatments on mortality in patients with schizophrenia underscores the difficulty in relating intermediate and distal outcomes (e.g., mortality) in comparison to proximal outcomes (e.g., symptom reduction or relapse prevention) to effects of specific treatments (Fig. 2). Such distal outcomes are multi-determined and several relevant outcome predictors are difficult to control or sometimes even to measure leading to less robust and inconsistent associations.

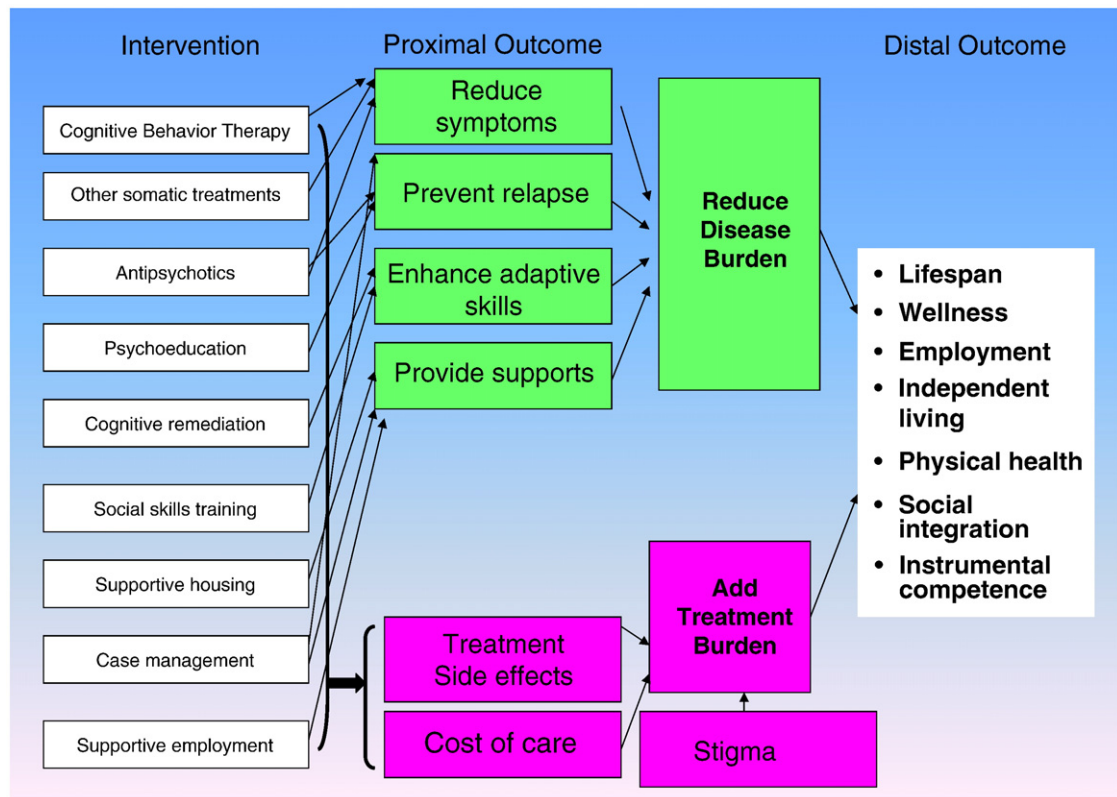


Fig. 2. Impact of treatment services on proximal and distal outcomes in schizophrenia.

2.5. Summary

Antipsychotic medications are effective in reducing overall symptoms and risk of relapse in patients with schizophrenia, with primary efficacy mainly against positive and disorganization symptom domains. Except for the greater efficacy of clozapine in treatment-refractory schizophrenia patients, differences in efficacy among other antipsychotic agents are relatively minor. In contrast to small differences in efficacy, antipsychotic agents differ substantially in their side-effect profiles. FGAs and SGAs both constitute very heterogeneous classes of antipsychotic medications without any definitive categorical boundary between them in terms of efficacy, safety, tolerability, or overall outcome. The broad distinction between SGAs and FGAs is the better ability of the former to provide an equivalent antipsychotic effect with a lower liability to cause EPS, although there is substantial variation within each class in this regard. Since there is no categorical difference between FGAs and SGAs, however, with reference to this or any other attribute, classification of antipsychotic agents into FGA and SGA classes has little value and should be abandoned (Fischer-Barnicol et al., 2008; Grunder et al., 2009). On the other hand, "atypicality" or the ability to provide a good antipsychotic effect without EPS is an important attribute, with substantial variation across patients and different agents (Meltzer et al., 1989; Chen and Tandon, 2009).

In view of the significant individual variability in drug pharmacokinetics and treatment responsivity, it should also

be emphasized that broadly equivalent efficacy across patient groups does not translate into equal efficacy in each individual patient (De Leon et al., 2005; Mauri et al., 2007; Stroup, 2007). There is no best agent or a best dose of any agent for all patients. Despite limited data regarding antipsychotic dose–response relationships, there appear to be specific dose ranges for these agents for optimal effectiveness (Gardos and Cole, 1973; Warchick et al., 2002; Kinon et al., 2004; Liu and De Haan, 2009; Gardner et al., 2010). It is not currently possible to prospectively predict which antipsychotic medication might be optimal for a given patient. Decisions about antipsychotic therapy consequently entail a trial-and-error process with careful monitoring of clinical response and adverse effects and an ongoing risk–benefit assessment and judicious switching if appropriate.

SGAs, introduced into clinical practice over the past twenty years, were initially considered to be much more effective than FGAs with a broad spectrum of efficacy against the wide array of symptoms in schizophrenia and with a significantly better safety and tolerability profile. With continuing utilization and research, they have been recognized to not substantially differ in efficacy from FGAs (with the exception of clozapine in treatment-refractory patients), less likely to cause EPS than FGAs but not completely devoid of that adverse effect, and otherwise associated with the same array of side-effects as FGAs.

Despite their shortcomings, both the initial introduction of FGAs in the 1950s and the subsequent introduction of SGAs in the 1990s represented meaningful steps in our efforts to

provide effective treatment for individuals with schizophrenia. Just as it is important not to exaggerate what existing treatments for schizophrenia can offer (Tyner and Kendall, 2009), however, it is equally important not to discount what they can do.

2.6. Other pharmacological agents

In view of the limitations of antipsychotic agents in the pharmacotherapy of various symptom domains of schizophrenia, several other psychotherapeutic medications have been utilized in its treatment. These include various anticonvulsants, antidepressants, benzodiazepines, and lithium. Whereas none of these treatments has been found to be consistently useful as monotherapy, some have provided modest benefits as adjuncts to antipsychotic medications in targeting specific symptom domains in some patients (Wolff-Menzler et al., 2010; Zink et al., 2010). Despite a paucity of data, anticonvulsant medications are extensively utilized in the treatment of schizophrenia as adjuncts to antipsychotic agents. Valproic acid, carbamazepine, and lamotrigine, the three most commonly used agents, have little utility as monotherapy but are inconsistently effective as adjuncts to antipsychotic agents in targeting aggression and impulsivity in patients with schizophrenia (Leucht et al., 2002; Basan et al., 2004; Tiihonen et al., 2009b). Adjunctive antidepressant medications are useful in targeting depressive and anxiety symptoms in patients with schizophrenia, particularly when they occur in the absence of prominent positive symptoms (Whitehead et al., 2003; Zisook et al., 2009) and may reduce craving among those with comorbid substance use disorders (Wobrock and Soyka, 2008). Benzodiazepines are commonly utilized as adjunctive treatments and are most useful in targeting anxiety, agitation, and insomnia (Wolkowitz and Pickar, 1991; Volz et al., 2007; Thomas et al., 2009). Lithium is ineffective as monotherapy and has limited utility as an adjunctive treatment (Lehman et al., 2004; Leucht et al., 2004). In general, evidence is weak at best for the effectiveness of pharmacological agents other than antipsychotics in the treatment of schizophrenia (Buchanan et al., 2010).

2.7. Electro-convulsive therapy and repetitive transcranial magnetic stimulation

The role of electroconvulsive therapy (ECT) in the treatment of schizophrenia has diminished over the past two decades. Although recent data are limited, ECT may augment antipsychotic efficacy in some patients and may provide a more rapid onset of antipsychotic action (Greenhalgh et al., 2005; Tharyan et al., 2005; Painuly and Chakrabarti, 2006; Chanpattana et al., 2010; Matheson et al., 2010). Electroconvulsive therapy is useful in treating catatonic symptoms in schizophrenia (Thirthalli et al., 2009) and as an adjunct to clozapine in some antipsychotic-refractory schizophrenia patients (Braga and Petrides, 2005).

Repetitive transcranial magnetic stimulation (rTMS) is showing some promise in treating different symptom domains in schizophrenia (principally negative symptoms and auditory hallucinations) using different frequencies and targeting different cortical regions (Aleman et al., 2007;

Freitas et al., 2009; Blumberger et al., 2010; Dlabac-de Lange et al., 2010). Data, however, are preliminary at this time.

Deep brain stimulation is another therapeutic modality with potential utility but virtually no data at this time (Mikell et al., 2009).

3. Psychotherapies and social treatments

Although antipsychotic medications are the mainstay of treatment for schizophrenia, pharmacotherapy alone produces only limited improvement in negative symptoms, cognitive function, social functioning and quality of life. Additionally, many patients continue to suffer from persistent positive symptoms and relapses particularly when they fail to adhere to prescribed medications. This underlines the need for multi-modal care including psychosocial therapies as adjuncts to antipsychotic medications to help alleviate symptoms and to improve adherence, social functioning and quality of life (Patterson and Leeuwenkamp, 2008; Kern et al., 2009). We briefly review evidence that has accumulated on the efficacy of the major modalities of psychosocial treatment (Table 4).

3.1. Psychoeducation and coping-oriented interventions

Psychoeducational interventions provide information about the disorder and its treatment to patients and their family members, and additionally inform the patients and family members about strategies to cope with schizophrenic illness (Hogarty et al., 1986). An extensive body of literature has accumulated regarding the efficacy of these interventions. Meta-analyses suggest that these interventions reduce high expressed emotion among relatives, and decrease relapse and rehospitalization rates (Brown et al., 1972; Mari and Streiner, 1994; Pitschel-Walz et al., 2001; Pilling et al., 2002a; Giron et al., 2010). In general, interventions that include family members are more effective (Pharaoh et al., 2006; Lincoln et al., 2007). Multi-family psychoeducation group approaches, which provide family psychoeducation and additionally offer an expanded social network, are found to reduce rates of relapse (McFarlane et al., 1995) as are peer-to-peer education programs for families and patients (Chien et al., 2006).

3.2. Cognitive Behavior Therapy (CBT)

About a third of patients with schizophrenia continue to suffer from persistent psychotic symptoms despite adequate pharmacotherapy. Cognitive Behavior Therapy (CBT) has emerged to address this need, and is based on the hypothesis that psychotic symptoms such as delusions and hallucinations stem from misinterpretations and irrational attributions caused by self-monitoring deficits. CBT seeks to help patients rationally appraise their experience of disease symptoms and how they respond to them, thereby reducing symptoms and preventing relapse (Turkington et al., 2008; Tai and Turkington, 2009). Meta-analytic evaluations have found CBT to be effective in ameliorating positive symptoms (Gould et al., 2001; Rector and Beck, 2001; Zimmermann et al., 2005; Pfammatter et al., 2006), although effect sizes of CBT have been noted to be inconsistent across studies. In fact, a recent

Table 4

Psychotherapeutic interventions in schizophrenia: effect sizes.

Treatment modality	Most commonly reported outcome variable	Effect size (Hedge's <i>g</i>)	References
Social skills training	Skill acquisition Community functioning	.76–1.43 .51	Benton and Schroeder, 1990; Pilling et al., 2002b; Kurtz and Mueser, 2008.
Psychoeducation	Relapse (2 years)	.17–.56	Pitschel-Walz et al., 2001; Pilling et al., 2002a; Lincoln et al., 2007
Cognitive Behavior Therapy (CBT)	Positive symptoms	.35–.65	Zimmerman et al., 2005; Pfammatter et al., 2006 ; Wykes et al., 2008.
Cognitive remediation	Cognitive functioning Social functioning	.11–.98 .36–.51	Pilling et al., 2002b; Krabbendam and Aleman, 2003; McGurk et al., 2007

meta-analysis of six blinded studies (Lynch et al., 2010) found CBT to be ineffective in reducing any symptoms of schizophrenia or in preventing relapse; the 'fairness' of this analysis has been questioned (Kingdon, 2010). Discrepant findings are explained by methodological variations in rater blinding, therapy time, and nonspecific effects (Tarrier and Wykes, 2004; Wykes et al., 2008). CBT is reported to be ineffective in targeting negative symptoms and its effects on other treatment domains are not well studied. Although CBT is recommended as a standard of care for persons with schizophrenia (NICE, 2009; Dixon et al., 2010), data from pragmatic studies suggest that its benefits are modest at best (Durham et al., 2005; Garety et al., 2008).

3.3. Cognitive remediation

A substantive proportion of schizophrenia patients have impaired cognition, particularly in the domains of psychomotor speed, attention, working memory and executive function, verbal learning and social cognition. These deficits are robust (~1 SD) and persist during the illness, and serve as rate limiting factors for functional recovery (Green, 1996; Tandon et al., 2009). Several cognitive remediation approaches have been developed over the past two decades which involve compensation strategies to organize information, use of environmental aids such as reminders and prompts, and a range of techniques designed to enhance executive function and social cognition (Velligan et al., 2006; Medalia and Choi, 2009; Eack et al., 2010). Earlier reviews and meta-analyses of this field suggested that cognitive remediation leads to modest improvements in performance on neuropsychological tests but has limited generalization to functional outcomes (Pilling et al., 2002b; Krabbendam and Aleman, 2003; Twamley et al., 2003; Dickinson et al., 2010). One large meta-analysis involving 1151 patients, McGurk et al. (2007), however, found that cognitive remediation was associated with significant improvements in cognitive performance and symptoms, as well as psychosocial functioning in schizophrenia. Cognitive remediation has been found to be more effective in studies that provided adjunctive psychiatric rehabilitation in addition to cognitive remediation. Studies vary in effect sizes and methodological rigor (Wykes and Huddy, 2009), however, and questions remain about the durability of benefits of cognitive remediation.

3.4. Social skills training (SST)

Schizophrenia patients manifest deficits in social competence and these contribute to poor outcome. The goal of SST is to improve day-to-day living skills by focusing on components of social competence such as self-care, basic conversation, vocational skills, and recreation. These skills are practiced mostly in group settings using techniques based on operant and social learning theory. Historically, token economy was the first such intervention that sought to improve the social behavior of patients with psychiatric illness. While effective, the results did not generalize beyond the therapeutic setting. During the 1980s and 90s, specific training approaches were developed to address each of the skill deficits and their application was found to be effective in improving social skills and reducing rates of relapse (Benton and Schroeder, 1990). A recent meta-analysis of randomized controlled trials of social skills training in schizophrenia showed a large effect size for improvement in skills, a moderate effect size for performance-based social and community skills and for community functioning, and a small effect size for symptoms and relapse (Kurtz and Mueser, 2008). In contrast, a recent Cochrane review (Tungpunkom and Nicol, 2008), however, failed to document benefits of life skills programs for persons with schizophrenia. More data are needed about predictors of response to social skills training in schizophrenia, and the durability and generalizability of therapeutic benefits.

3.5. Assertive community treatment (ACT)

Assertive community treatment offers an approach to integrated delivery of clinical services to patients with schizophrenia using a multidisciplinary approach, high frequency of patient contact, low patient-to-staff ratios, and outreach to patients in the community. ACT, compared to routine care, has been found to significantly reduce hospitalizations and improve housing stability (Bond, 1995; Bustillo et al., 2001; Coldwell and Bender, 2007; Nelson et al., 2007). ACT appears most effective among patients with high baseline rates of hospitalization (Marshall and Lockwood, 1998). However, not all studies show ACT to be effective and its efficacy outside the USA has not been firmly established (Burns et al., 2007). Although ACT appears to be an effective method of treatment delivery, the critical

components which contribute to its benefits have not been precisely defined.

3.6. Supported employment

Supported employment involves individually tailored job placement, rapid job search, provision of ongoing job supports, and integration of vocational and mental health services. There is evidence that supported employment is a more effective approach to help patients find and maintain competitive employment than traditional approaches to vocational rehabilitation (Campbell et al., 2009; Dixon et al., 2010). However, long-term job retention and economic independence have not been clearly shown with supported employment (Lehman et al., 2002).

3.7. Summary

In summary, research on psychosocial approaches to treatment of schizophrenia has yielded incremental evidence of efficacy of CBT, SST, family psychoeducation, ACT and supported employment. These interventions are therefore recommended for clinical application in the recently published Schizophrenia Patient Outcomes Research Team guidelines (PORT, Dixon et al., 2010) which provide a comprehensive review of current evidence-based psychosocial interventions for schizophrenia. Relatively few rigorously conducted trials of psychosocial interventions have been reported in the early course of schizophrenia, a phase of the illness when effective interventions may yield long-term outcome benefits (Penn et al., 2005).

Other psychotherapeutic approaches such as peer support services, personal therapy, and motivational interviewing to improve adherence are promising but are yet to yield systematic evidence in support (Lehman et al., 1993; Hogarty et al., 1997). There is little evidence for the efficacy of psychodynamic therapies in schizophrenia (Malmberg et al., 2009).

More hypothesis-driven research is needed to examine active ingredients of the therapeutic modalities that work, to identify the synergistic effects of combinations of interventions, and to assess their cost-effectiveness.

4. Current deficiencies and approaches to address them

Pharmacological, psychological, and social treatments for schizophrenia have evolved over the past two decades, generating much excitement but only modest improvements in the lives of people with schizophrenia. In significant part, this is due to the limited availability and access to the broad range of effective treatments and their inconsistent application. Additionally, existing treatments are incompletely effective and associated with a range of adverse effects. Furthermore, by the time most patients with the illness present to the clinic for treatment, the pathology of schizophrenia has often advanced to such a degree that its course is difficult to reverse. Finally, the significant variations in the way patients respond to different treatments, without the ability to predict how a particular individual will respond, makes optimal personalized therapy difficult.

Major barriers to our ability in developing more effective treatments include limiting ourselves to a “pharmacological

magic bullet” approach heavily dependent on dopamine D-2 antagonism, reliance on serendipity, failure to critically examine alleged “major advances”, and inability to fully apply the emerging understanding of the clinical nature and neurobiology of the disorder (Carpenter and Koenig, 2008; Lewis and Sweet, 2009). We believe that our current state of knowledge about the etiology, pathophysiology, and clinical expression of schizophrenia (Tandon et al., 2008b; Keshavan et al., 2008; Tandon et al., 2009) allows us to better define molecular and clinical treatment targets, develop approaches to prevent disease progression at different stages of the disorder, and personalize treatment based on individual characteristics. We summarize the current status of approaches to address the many unmet needs in the treatment of schizophrenia and examine their promise and potential pitfalls.

While the several limitations in our current therapeutic armamentarium are obvious, it is also clear that “usual treatment” generally falls far short of what can be achieved. Here, we first evaluate the challenges in bridging the science-to-service gap in schizophrenia treatment and suggest approaches to implement evidence-based individualized treatment.

4.1. Bridging the efficacy–effectiveness gap

The difficulty in translating the range of pharmacological (Buchanan et al., 2010) and psychosocial (Dixon et al., 2010) evidence-based treatments for schizophrenia into better outcomes for persons with schizophrenia is underscored by the marked variation in treatment practices and the gap between the possibilities offered by the range of available treatments and the “usual treatment” actually provided. Even as the focus in the treatment of patients with schizophrenia has moved from palliation and symptom control to functional improvement and recovery (Nasrallah et al., 2005; Davidson et al., 2009a; Harvey and Bellack, 2009; Remington et al., 2010), the vast majority of patients do not receive evidence-based treatment which could reduce disability and optimize quality of life (Bollini et al., 2008; Drake et al., 2009; Mojtabai et al., 2009). Key practices that can help reduce the efficacy–effectiveness gap include:

- (i) knowledge about what different treatments can and cannot do and the practice of evidence-based medicine (Drake et al., 2009).
- (ii) precise definition of treatment targets for patients based on informed personal preferences, individual vulnerabilities and needs (Tandon et al., 2006; Davidson et al., 2009a).
- (iii) measuring the full impact (benefit to risk ratio) of individual treatments in each patient by the practice of measurement-based care (Tandon et al., 2008c) in conjunction with a protocol-based approach to such measurement (Marder et al., 2004; De Hert et al., 2009).
- (iv) collaborative and informed decision-making on an ongoing basis, evaluating patient needs and preferences, measured effects of current treatments, and available treatment options at each stage (Levander et al., 2007; Mistler and Drake, 2008).

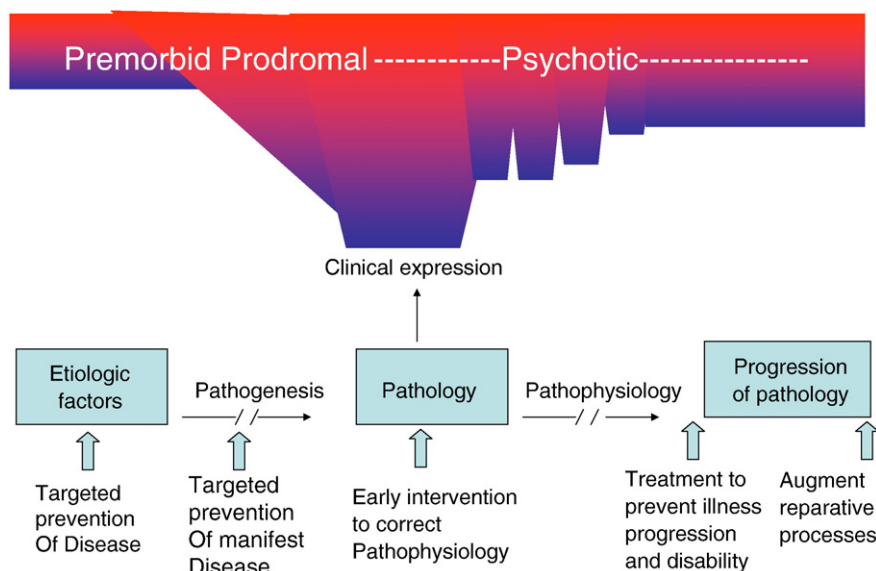


Fig. 3. Stages of schizophrenic illness: opportunities for disease modification.

4.2. Development of future treatments: towards rational discovery based on understanding of biology and clinical expression of schizophrenia

New pharmacological treatments for schizophrenia have thus far been developed on the basis of serendipity, trial and error, and using models based on existing antipsychotic medications which is why all available antipsychotic agents today are D-2 antagonists. Our current understanding of the etiology and pathophysiology of schizophrenia (Keshavan et al., 2008; Tandon et al., 2008b) allows us to begin targeting several steps in the pathogenesis of the disorder (Fig. 3) and rationally defining cellular and molecular targets other than the D-2 receptor (Table 5). Drug development for schizophrenia has also thus far been predicated on finding the “magic bullet” that effectively addresses all aspects of its psychopathology. Our current understanding of the distinct domains of psychopathology (Carpenter and Koenig, 2008; Tandon et al., 2009) allows us to develop different treatments specifically targeted at individual symptom dimensions of schizophrenia rather than a single treatment for all the disparate symptoms.

4.3. Targeting psychopathological dimensions of schizophrenia

Until now, efforts to identify an effective anti-schizophrenia medication have been directed towards developing a broad-spectrum, disease-specific panacea that would target all relevant symptom domains. Current antipsychotic agents are much more effective in reducing positive symptoms and disorganization than negative or cognitive symptoms. Specific pharmacological strategies directed at each of these other symptom domains are currently under investigation (Kim et al., 2009).

4.4. Specific treatments for negative symptoms

Persistent negative symptoms are a major reason for the significant debilitation associated with schizophrenia and current treatments have only limited efficacy on this domain (Kirkpatrick et al., 2006). Several pharmacological strategies to specifically treat negative symptoms have been evaluated with limited success thus far. Over the past decade, agents that stimulate the N-methyl-D-aspartate (NMDA) glutamate receptor have been studied and partial and full agonists at the glycine site have been used in conjunction with the antipsychotics with some success in reducing negative symptoms. Agents that activate the metabotropic glutamate 2/3 receptors have also shown some promise in ameliorating negative symptoms (Patil et al., 2007).

4.5. Specific treatments for cognitive deficits

Perhaps, to an even greater extent than negative symptoms, cognitive dysfunction is correlated with social and vocational impairment in schizophrenia. Two major initiatives (Measurement and Treatment Research to Improve Cognition in Schizophrenia [MATRICS], Marder and Fenton, 2004; and Cognitive Neuroscience approaches to the Treatment of Impaired Cognition in Schizophrenia [CNTRICS], Barch et al., 2009) have been undertaken by the National Institute of Mental Health in the USA to develop effective treatments for the cognitive deficits of schizophrenia. While several neuropharmacological mechanisms have been proposed to explain the cognitive impairments in schizophrenia, none is considered definitive at present. Several pharmacological approaches to ameliorate cognitive impairments in schizophrenia are currently under study – these include alpha-7 nicotinic receptor agonists, dopamine-1 receptor

agonists, NMDA glutamate receptor agonists, modulators of the glutamatergic AMPA receptor, metabotropic glutamate receptor agonists, muscarinic receptor agonists, 5-HT_{1A} agonist strategies, and phosphodiesterase 10 inhibitors (Harvey, 2009).

4.6. Phase-specific treatment strategies

Although different pathophysiological processes appear to be relevant at different stages of schizophrenia, current treatment does not vary across the course of the illness. Phase-specific interventions in schizophrenia are predicated on three key principles. First, while schizophrenia begins in adolescence or early adulthood, its seeds are believed to be planted earlier in a long-term neurodevelopmental process eventually leading to deviant brain structure and function. We recognize that multiple and sequential etiological factors may interactively and additively contribute to the progressive emergence of the full clinical phenotype of the illness (Keshavan et al., 2008). This view suggests that prevention and intervention could be tailored to the stage of evolution of the disease processes in individuals predisposed to the disorder. Identification of risk factors and symptomatic indicators are critical for accurately selecting at-risk people and matching them to the most appropriate preventive treatment. Second, as proposed in the critical period hypothesis (Birchwood et al., 1998), therapeutic interventions are most effective if they are administered during critical periods of vulnerability early in the course of the illness. Third, therapeutic interventions must consider the substantial role of altered neuroplasticity in the pathogenesis of schizophrenia (Lewis and Gonzalez-Burgos, 2008; Krystal et al., 2009) and the need to reverse this altered plasticity by neuro-biological and psychotherapeutic interventions (Eisch et al., 2008; Fisher et al., 2009).

Using the Mrazek and Haggerty (1994) model, no specific population-level prevention efforts (akin to preventing dental caries by fluoride supplementation) are currently available (Mojtabai et al., 2003; McGrath, 2010) and selective prevention aimed at asymptomatic high-risk subgroups is only a hope (Compton, 2004). In the future, such interventions may be feasible in the premorbid phase by early recognition of risk factors for the illness and prevention of the development of behavioral or cognitive pathology by the use of targeted approaches if specific effective treatments were available (Fig. 3) (National Research Council and Institute of Medicine, 2009).

In the next stage, the prodromal phase, indicated prevention may be possible by treating sub-threshold symptoms to reduce risk for a more severe disorder: the goal thus far has been prevention of “conversion” to psychosis (Yung et al., 2007). Several approaches to defining and treating the schizophrenia prodrome have been evaluated (McGorry et al., 2009) — treatments studied include antipsychotics (McGorry et al., 2002; McGlashan et al., 2006), antidepressants (Cornblatt et al., 2007), omega 3 fatty acids (Amminger et al., 2010), and cognitive behavior therapy (Morrison et al., 2004). Early results are promising, but questions remain about the precise definition of prodromal schizophrenia and the risk/benefits of this approach including the possibility of unnecessary interventions in individuals who might turn out

to be false-positive (Marshall and Rathbone, 2006; Gaebel and Riesbeck, 2007; de Koning et al., 2009; Ruhrmann et al., 2009; Bosanac et al., 2010).

With the onset of psychotic symptomatology, the objective would be early identification of the illness and prompt initiation of effective treatment might avert disease progression and limit deterioration in social function (Loebel et al., 1992; Wyatt and Hunter, 2001; Perkins et al., 2005; Lieberman et al., 2006; Salokangas and McGlashan, 2008; Alvarez-Jimenez et al., in press). During later stages of the illness, goals of therapy include the optimal reduction of psychopathology and possible reversal of brain pathology.

At all stages of illness, the principal objective is the maximal restoration of function (Fig. 1). In contrast to the current practice of utilizing the same approach throughout the illness, treatments in the future should optimally be phase-specific to the stage of the illness in which the patients present (Tandon et al., 2009).

4.7. Other pharmacological targets

All current antipsychotic therapies have been developed on the half-century old platform of dopamine D₂ receptor antagonism. The potent serotonin 5HT_{2A} antagonism characteristic of the more recently developed so-called second-generation antipsychotic agents is associated with a lower risk of neuromotor side-effects (EPS and tardive dyskinesia). In view of the therapeutic limitations of these approaches, a range of other molecular and cellular strategies are being evaluated in schizophrenia. In addition to other dopamine and serotonin receptors, a variety of glutamatergic, cholinergic, gaba-ergic, neuropeptidergic, cannabinoid, and non-neurotransmitter receptor targets are also being studied in the treatment of schizophrenia. The current status of these approaches along with a listing of specific candidate agents is summarized in Table 5.

4.8. Towards personalized therapy

Persons with schizophrenia demonstrate extremely varied responses to different therapeutic interventions. This heterogeneity in treatment responsivity is influenced by age, gender, race, genetic and environmental factors, social conditions and comorbidities. The current inability to predict individual response necessitates a trial-and-error treatment strategy. Significant recent advances in genetics and molecular neurobiology have led to considerable enthusiasm about the potential of applying these strategies to upgrade the treatment of schizophrenia (Arranz and Kapur, 2008; Gerretsen et al., 2009). Given the significant inter-individual variation in response to antipsychotic drug treatment, a variety of pharmacogenetic studies are being conducted; in particular, studies of the role of 5HT_{2A} and 5HT_{2C} receptor polymorphisms in predicting specific antipsychotic response are promising (Reynolds, 2007). While some studies have focused on predicting therapeutic response to clozapine and other treatment (Volpi et al., 2009), other molecular genetic investigations are directed at predicting side-effects of antipsychotic treatment such as tardive dyskinesia (Basile et al., 2002). These efforts are still exploratory, however, and the translation of genotype-based molecular explanation to

Table 5

Molecular target	Psycho-pathological target	Mode of action rationale	Agents being studied	Current status of development
Dopamine <i>D-1 agonism</i> Zhang et al. (2009)	Cognitive deficits	Add-on to antipsychotic Improvement in executive function with dopaminergic stimulation in prefrontal cortex (PFC) Monotherapy	Dihydropyridine SKF-81297 Adrogolide Stepholidine Cariprazine	Preclinical to Phase II Mixed results thus far
<i>D-3 antagonism</i> Marino et al. (2008) Kiss et al. (2010)	Schizophrenia Psychosis Negative symptoms Cognitive sx	More selective anti-psychotic effect than D-2 blockade Possible benefits for negative sx and cognition	A-706149 BTS-79018 U 99194A SB-277011 SB-414796 SB-773812 PNU 177864 LU 201640 NGD-94-1	Preclinical to Phase II Benefits in clinical populations not shown thus far
<i>D-4 antagonism</i> Marino et al. (2008)	Schizophrenia Psychosis	Monotherapy Relatively greater affinity of clozapine for D-4 receptor	ACR-325 Aplindore SSR-181507 WS-50030 Cariprazine OPC-34712 Modafinil Armodafinil Lisdexamfetamine Tolcapone Entacapone PGX 200097	Preclinical to Phase II Negative findings with D-4 blockers like sonepiprazole, fananserin, and belaperidone. Diminishing interest. Preclinical to Phase III Challenges in getting intrinsic activity “just right” for optimal efficacy and tolerability for each candidate.
<i>D-2 partial agonism</i> Brennan et al. (2010) Jackson et al. (2010)	Schizophrenia Psychosis Cognition	Monotherapy Similar to currently available aripiprazole	GSK-3 inhibitor AR-014418	Preclinical to Phase II Benefits in clinical populations not shown thus far
Dopamine-releasing agents Marino et al. (2008)	Cognition Negative symptoms	Add-on to antipsychotic Improvement in executive function with dopaminergic stimulation in PFC	Modafinil Armodafinil Lisdexamfetamine Tolcapone Entacapone PGX 200097	Preclinical to Phase II Mixed results thus far
Catechol-O- methyltransferase (COMT) inhibitors Roussos et al. (2009)	Cognition	Add-on to antipsychotic. Improvement in executive function with dopaminergic stimulation in prefrontal cortex. In PFC, COMT breaks down dopamine	Entacapone PGX 200097	Preclinical to Phase II Benefits in clinical populations not shown thus far
Dopamine signaling pathways Freyberg et al. (2010)	Cognition Psychosis	Exploratory	GSK-3 inhibitor AR-014418	Preclinical Benefits in clinical populations not shown thus far
Serotonin <i>D-2/5HT2A antagonists</i> Meyer et al. (2009)	Psychosis with reduced EPS liability	Monotherapy Similar to currently available ‘SGAs’ with fewer other side-effects	Lurasidone Ocapiridone GMC-283 ORG-23365 GSK-773812 Lu-31-130 YKP-1358 ZD-3638 QF 2004B SLV-313 SLV-314	Phase I to Phase III Lurasidone appears similar to currently available ‘SGAs’ Continuing interest in developing a “better SGA” with fewer side-effects
<i>D-2 antagonist + 5HT1A agonist</i>	Psychosis with additional benefits on cognition and negative symptoms	Monotherapy Property of some ‘SGAs’.	SLV-313 SLV-314	Preclinical to Phase II Benefits in clinical populations not shown thus far

McCreary and Jones, (2010) Neves et al. (2010)		Modulation of PFC dopamine	Abaperidone PD-158771 SSR-181507 LASSBio-664 F 15063 SLV-310 HMR-2934 ITI-007 Tetrahydro-carbazole Pimavanserin ACP-103	Preclinical to Phase II Benefits in clinical populations not shown thus far
<i>D-2 antagonist + 5HT reuptake inhibition</i> Marino et al. (2008)	Psychosis with additional benefits on cognition and negative symptoms	Monotherapy Modulation of dopamine tone		
<i>5HT-2A inverse agonist</i> Aloyo et al. (2009) Meltzer et al. (2010)	Augment speed or degree of antipsychotic effect and reduce EPS	Add-on to antipsychotic treatment Build on 5HT2A antagonism		Phase II Mixed results thus far
<i>5HT-2C agonists</i> Kozikowski et al. (in press)	Psychosis without EPS liability	Monotherapy Agents inhibit dopamine release in mesolimbic + mesocortical pathways	Pruvanserin CYR-101 Vabicaserin WAY-163909 RO60-0175 VER-2692 Eplivanserin	Preclinical to Phase II Benefits in clinical populations not shown thus far
<i>5HT 2A/2C antagonists</i> Marino et al. (2008) <i>5HT-6 antagonists</i> Rosse and Schaffhauser (2010)	Psychosis without EPS liability Cognitive deficits in schizophrenia	Monotherapy Efficacy of “SGAs” Add-on to antipsychotic treatment Modulation of dopamine tone	PRX-07034 SUVN-502 Lu-AE-58054 SGS-518	Phase I to III Not found to be efficacious Preclinical to Phase II Benefits in clinical populations not shown thus far
Glutamate <i>NMDA antagonists</i> Lieberman et al. (2009)	Cognitive symptoms	Add-on to antipsychotic treatment Therapeutic agent for Alzheimer's disease	Memantine Riluzole	Phase III Benefits in clinical populations not shown thus far
Glycinergic agents Labrie and Roder (2010)	Psychosis, negative symptoms, cognitive symptoms	Add-on to antipsychotic Enhance NMDA activity	D-cycloserine Glycine D-serine Nebostinel Neboglamine AZD 8529	Phase II to III Mixed results thus far
<i>Glycine transporter 1 (GlyT1) inhibitors</i> Javitt (2009)	Psychosis, negative symptoms, cognitive symptoms	Add-on and monotherapy Enhance NMDA activity via allosteric glycine site	Sarcosine ORG-24461 SSR-103800 SSR-504734 GSK-1018921 R-1678 R-4996 R-231857 PF-3311945 PF-3463275 SCH 900435	Preclinical to Phase-II Mixed results thus far. Significant interest in this class of drugs at this time.
<i>D amino-acid oxidase (DAAO) inhibitors</i>	Psychosis, negative symptoms, cognitive symptoms	Add-on to antipsychotic	ASO 57278 DAAOI-1 4H furo-pyrrole -5 carboxylic acid	Preclinical to phase 2

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Table 5 (continued)

Molecular target	Psycho-pathological target	Mode of action rationale	Agents being studied	Current status of development
Metabotropic glutamate 2/3 agonists Patil et al. (2007) Conn et al. (2009)	Psychosis Cognition	Monotherapy Antipsychotic activity in animal models	LY-2140023 LY-341495 LY-404039	Phase I to Phase III Mixed results
Metabotropic glutamate 1/5 agonists Kanuma et al. (2010) Lesage and Steckler (2010)	Negative symptoms Psychosis Cognition	Monotherapy Antipsychotic activity in animal models	ADX-47273 ADX-63365 ADX-71149 AZD-9272	Preclinical to Phase I Benefits in clinical populations not shown thus far
Metabotropic glutamate 1/5 antagonists Lesage and Steckler (2010)	Cognitive deficits	Add-on to antipsychotic Benefit in animal model	Acamprosate MGS 0039 JNJ-16567083 NBI-59159	Preclinical to Phase 2 Preliminary. No good clinical data.
Glutamate transport inhibitors	Psychosis	Monotherapy Antipsychotic activity in animal models		Preclinical
N-Acetyl-L-aspartyl- L-glutamate (NAAG) peptidase inhibitors	Psychosis Cognition	Monotherapy Increase mGlu 2/3 activity	GPI-5693 ZJ-38	Phase I to II Benefits in clinical populations not shown
AMPA receptor agonists	Cognition Negative symptoms	Add-on	Fanampator GSK 729327 ORG 24448 LY 404187 IRA-21 LY-326325	Preclinical to Phase II Benefits in clinical populations not shown thus far
AMPA/kainate receptor antagonists	Psychosis Cognition	Monotherapy		Preclinical Benefits in clinical populations not shown thus far
Cholinergic Muscarinic agonists Raedler et al. (2007) Bradley et al. (2010) Leach et al. (2010) Money et al. (2010)	Psychosis Cognition	Monotherapy	N-desmethyl-clozapine GSK-1034702 Xanomeline Sabcomeline AC260584 LY-2033298 NGX-267	Preclinical to Phase III Mixed results thus far
Nicotinic agonists Haydar and Dunlop (2010) Money et al. (2010)	Cognition	Add-on therapy Implication of nicotinic mechanisms in patho-physiology	Varenicline Isopronicline EVP-6124 MEM-3454 MEM-63908 ABT-089 GTS-21 SSR-180711 W-56203 PNU-120596 PH-399733 TC-5619 WAY-317538	Preclinical to Phase III Clear benefits in clinical populations not shown thus far

Nicotine receptor antagonist	Cognition	Add-on therapy	Mecamyl-amine	Phase II Benefits not shown
Gaba GABA agonists Charych et al. (2009) Geffen et al. (2009)	Cognition Psychosis	Add-on and monotherapy	MK-0777 BL-1020 L-830982 Tiagabine	Phases I to III Mixed results thus far
Assorted Alpha-2 Adrenoreceptor antagonists	Psychosis Mood symptoms Cognition	Add-on to antipsychotic	Idazoxan Dexefaroxan ORM-10921 ORM-12471 Rolipram Papaverine IC 200214 MP-10 WEB-3 NPD-001 PF-2545920 Cilomilast AWD12-281	Phase II No clear benefits shown in clinical populations.
Phosphodi-esterase PDE4 and 10A inhibitors Schmidt et al. (2008) Sluciak (2008) Grauer et al. (2009) Verhoest et al. (2009)	Psychosis Cognition	Monotherapy and add-on		Preclinical to Phase II No benefits shown in clinical populations
Histamine H-3 antagonists Tiligada et al. (2009)	Cognition	Add-on therapy to antipsychotic.	PF-3654746 GSK-189254 GSK-207040 BF2.649 A-668057 JNJ-1081457 ABT 239 MK 0249 MK-0557 AL-108 Osanetant Talnetant AZD 2624 AVE-1625 SLV-319 Cannabidiol	Preclinical to Phase II No benefits shown in clinical populations
Neuropeptide-Y antagonist	Cognition Psychosis	Add-on and monotherapy		Phase II No benefits thus far
Neurokinin-3 antagonists Dawson and Smith (2010)	Psychosis Cognition	Monotherapy and add-on		Phase II Mixed results so far
Cannabinoid receptor antagonists Roser et al. (2010)	Psychosis Cognition	Monotherapy and add-on Cannabis precipitates psychotic symptoms		Preclinical to Phase II Benefits in clinical populations not shown thus far
Neurosteroids and selective estrogen receptor modulators Bortolato et al. (2008) Ritsner (2010)	Psychosis Cognition Negative symptoms	Add-on More benign course in women	Dehydroepiandrosterone DHEA Estradiol Pregnelonone Raloxifene Finasteride	No consistent benefits

(continued on next page)

Table 5 (continued)

Molecular target	Psycho-pathological target	Mode of action rationale	Agents being studied	Current status of development
<i>Anti-inflammatory agents</i> Muller (2010)	Psychosis Early psychosis	Add-on to antipsychotic	Cyclooxygenase-2 inhibitor Celecoxib GSK 644784 Phospholipase inhibitors Miraxion and Curcumin Allopurinol Dipyramidole Propento-fylline TRK-820	Phase II to Phase III No clear benefits shown in clinical populations Phase I to Phase II No clear benefits shown in clinical populations Preclinical
<i>Adenosine agonists</i>	Psychosis Cognition	Add-on Purine hypothesis of schizophrenia		Preclinical to Phase II
<i>Kappa-opioid agonists</i> Yoshikawa et al. (2009)	Psychosis	Add-on to antipsychotic Role in regulating brain DA and 5-HT release		Preclinical
<i>Methyltransferase and histone deacetylase inhibitors</i> Deutch et al. (2008) Grayson et al. (2010)	Psychosis	Add-on to antipsychotic Epigenetic strategies to alter gene expression		Preclinical to Phase II
<i>Antibiotics and antiviral agents</i> Fatemi (2009) Levkovitz et al. (2010)	Psychosis	Add-on to antipsychotic Infectious theories of schizophrenia	Minocycline Valacyclovir Ceftriaxone	Benefits in clinical populations not shown thus far Phase I to Phase II No clear benefits thus far
<i>Retinoids</i>	Cognition	Add-on to antipsychotic	Bexarotene	Phase II
<i>MAO-B inhibitors</i>	Psychosis Cognition	Add-on to antipsychotic	Fenretinide Rasagiline	No benefits thus far No benefits thus far

Patil et al., 2007; Raedler et al., 2007; Bortolato et al., 2008; Deutch et al., 2008; Marino et al., 2008; Schmidt et al., 2008; Sluciak, 2008; Aloyo et al., 2009; Charych et al., 2009; Conn et al., 2009; Elmer and Kafkaki, 2009; Fatemi, 2009; Gaspar et al., 2009; Geffen et al., 2009; Grauer et al., 2009; Markou et al., 2009; Meyer et al., 2009; Rogers and Goldsmith, 2009; Yoshikawa et al., 2009; Bradley et al., 2010; Brennan et al., 2010; Dawson and Smith, 2010; Freyberg et al., 2010; Grayson et al., 2010; Haydar and Dunlop, 2010; Jackson et al., 2010; Kanuma et al., 2010; Labrie and Roder, 2010; Leach et al., 2010; McCreary and Jones, 2010; Meltzer et al., 2010; Mikkelsen et al., 2010; Money et al., 2010; Muller, 2010; Roser et al., 2010; Rosse and Schaffhauser, 2010; Verhoest et al., 2009.

reliable individual clinical prediction has been difficult because of the multifactorial determination of therapeutic response and the incomplete understanding of the clinical moderators of treatment response (de Leon, 2009; Blanc et al., 2010; Zandi and Judy, 2010).

Genomic advances also provide a powerful technique to dissect and hopefully clarify the heterogeneity of schizophrenia. Most experts believe that schizophrenia is not one disease, but many distinct diseases with overlapping symptomatology. Advances in genomics will facilitate the identification of gene products involved in the pathophysiology of schizophrenia and thereby enable the development of specific therapeutic agents directed at such “disease-specific” targets. While these techniques have great potential, their specific application towards improving treatment of schizophrenia is still at a preliminary stage.

5. Conclusions

The big picture view of the treatment of schizophrenia over the past quarter century draws several conclusions. First, an important paradigm shift has occurred toward early intervention in schizophrenia beginning with the prodrome in the illness (McGorry et al., 2009). Second, the focus of treatment has expanded beyond psychotic symptoms to include key clinical dimensions such as cognition deficits and negative symptoms as critical targets (Marder and Fenton, 2004; Kirkpatrick et al., 2006; Carpenter and Koenig, 2008; Tandon et al., 2009). Third, drug discovery in schizophrenia has moved beyond traditional dopamine D₂ and serotonin_{2A} antagonism (Patil et al., 2007; Raedler et al., 2007; Marino et al., 2008; Charych et al., 2009; Gaspar et al., 2009; Rogers and Goldsmith, 2009; Haydar and Dunlop, 2010; McCreary and Jones, 2010). Fourth, research is intensifying on the possible utility of several evidence-based psychotherapy modalities in combination with pharmacological approaches and even in monotherapy (Kern et al., 2009). Fifth, there has been a shift of focus from the efficacy to the effectiveness of treatments, and from merely suppressing symptoms to disease-modifying approaches, quality of life and restoration of function (Krystal et al., 2009). Sixth, outcome targets are being reformulated from stabilization with residual symptoms to quantifiable states of remission and recovery (Andreasen et al., 2005). Seventh, the discovery of new etio-pathophysiological mechanisms of disease causation should help deconstruct schizophrenia into gene-endophenotype elements linked to therapeutically meaningful clinical dimensions and offer novel targets for drug development (Thaker, 2007; Keshavan et al., 2008). Eighth, advances in pharmacogenomics bear the promise of better explaining the extreme variability in treatment outcomes across patients and providing individualized predictive markers of response or adverse effects (DeLeon, 2009; Gerretsen et al., 2009).

In order to avail of these opportunities to meaningfully advance the treatment of schizophrenia, it is essential to apply an attitude of hopeful scepticism, adopt a rigorous hypothesis-testing approach, and utilize appropriate methods. Both the promise and potential pitfalls have been reviewed in several recent publications (Carpenter and Koenig, 2008; Marino et al., 2008; Baloyianni and Tsangaris, 2009; Elmer and Kafkaki, 2009; Gerretsen et al., 2009;

Hughes, 2009; Insel, 2009; Markou et al., 2009; Mikkelsen et al., 2010; Porsolt et al., 2010; Takano, 2010).

Role of funding source

This manuscript was independently prepared by the authors: Rajiv Tandon, Matcheri S. Keshavan, and Henry A. Nasrallah without any external funding.

Contributors

Contributors to research, conceptualization, and writing of the manuscript: Rajiv Tandon, Matcheri S. Keshavan, and Henry A. Nasrallah.

Conflict of interest

This manuscript was independently produced by Rajiv Tandon, Matcheri S. Keshavan, and Henry A. Nasrallah.

Acknowledgements

We acknowledge our many teachers, colleagues, and students from whom we have learned much and are grateful to the tens of thousands of our patients who continually remind us of what we need to accomplish in our treatment of schizophrenia.

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