Antipsychotics in the Treatment of Bipolar Disorder

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Abstract Atypical antipsychotics have an important role in the acute and maintenance treatment of bipolar disorder. While robust evidence supports the efficacy of these agents in the treatment of mania and in the prevention of manic relapse, few atypical antipsychotics have shown efficacy in the treatment or prevention of depressive episodes. These agents pose a lower risk of extrapyramidal side effects compared to typical neuroleptics, but carry a significant liability for weight gain

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G. Gross and M.A. Geyer (eds.), *Current Antipsychotics*, Handbook of Experimental Pharmacology 212, DOI 10.1007/978-3-642-25761-2_8,

and other metabolic side effects such as hyperglycemia and hyperlipidemia. More comparative effectiveness studies are needed to assess the optimal treatment regimens, including the relative benefits and risks of antipsychotics versus mood stabilizers. The exploration of the molecular mechanisms of antipsychotics has helped to shed further light on the underlying neurobiology of bipolar disorder, since these compounds target systems thought to be key to the pathophysiology of bipolar disorder. In addition to modulating monoaminergic neurotransmission, atypical antipsychotics appear to share properties with mood-stabilizing agents known to alter intracellular signal transduction leading to changes in neuronal activity and gene expression. Atypical antipsychotic drugs have been shown to exhibit neuroprotective properties that are mediated by upregulation of trophic and cellular resilience factors. Building on our understanding of existing therapeutics, especially as it relates to underlying disease pathology, newer "plasticity enhancing" strategies hold promise for future treatments of bipolar disorder.

Keywords Bipolar disorder • Atypical antipsychotics • Monoamines • Signal transduction • Cellular resilience • Neuroplasticity

1 Introduction

Bipolar disorder is a common, chronic, recurrent mental illness that affects the lives and functioning of millions of individuals worldwide. High rates of relapse, chronicity, lingering residual symptoms, sub-syndromes, cognitive and functional impairments, psychosocial disability, and diminished well-being are unfortunately common occurrences in bipolar disorder (Goodwin and Jamison 2007; Levy and Manove 2011). Recent studies have shown the efficacy of several atypical antipsychotics, both as monotherapy and in combination with mood stabilizers such as lithium and valproate, for the treatment of acute mania, manic relapse prevention, and acute bipolar depression (Calabrese et al. 2005a, b; Surja et al. 2006; Thase et al. 2006; Tohen and Vieta 2009).

In this review, we discuss contemporary research with antipsychotics in bipolar disorder including clinical treatment, neuroimaging, genetic association studies, and molecular and preclinical pharmacological studies. This research has elucidated some of the cellular and molecular effects of antipsychotics that include their antidopaminergic effects, as well as other mechanisms of action. We conclude by highlighting key achievements, shortcomings and unmet medical needs, as well as emerging new targets and next steps forward. An understanding of the neurobiology of this complicated and multifactorial disease is still developing, yet critical for the future development of targeted therapies.

2 Clinical Studies

2.1 Introduction to Clinical Studies

Antipsychotic medications have a long history in the treatment of bipolar disorder, especially in the management of acute mania and depressive episodes with psychotic features (Gentile 2007). Conventional antipsychotics, such as chlorpromazine and haloperidol, have been reported to be effective in up to 70 % of patients with acute mania, particularly in those with psychomotor agitation (Cousins and Young 2007; Tohen and Vieta 2009; Vestergaard 1992). Additionally, retrospective reports suggest that conventional agents are effective in the maintenance treatment of bipolar disorder (Cousins and Young 2007). While efficacious, use of these drugs has been limited by their neurological side effects. These untoward effects may be of particular concern in bipolar disorder, as patients with affective illness appear to be especially vulnerable to acute extrapyramidal side effects and tardive dyskinesia (Gao et al. 2008). Further, several reports suggest that conventional antipsychotics have depressogenic potential (Kusumakar 2002).

The introduction of atypical antipsychotics held the promise of fewer neurological side effects and the potential for greater utility in bipolar disorder. Over the past decade nearly all of the drugs within this class have been systematically studied, either as monotherapy or adjunctive therapy to a mood stabilizer, both in acute mania as well as in maintenance therapy (Tables 1 and 3). As a result, most of these agents have been approved for these indications by health authorities around the world. More recently, some of these agents have been studied in bipolar depression (Tables 1 and 3). Current treatment guidelines include atypical antipsychotics as first-line treatment in bipolar disorder (APA 2002; Beckford-Ball 2006; Giese 2009; Toprac et al. 2006).

Despite the widespread use of atypical antipsychotics in bipolar disorder, there are limited data on the relative efficacy of (1) the various agents within the class; (2) atypical versus conventional antipsychotics; and (3) atypical antipsychotics compared to mood stabilizers, such as lithium or valproate. Likewise, there are little data on the comparative safety of atypical antipsychotics in this patient population. This section provides a review of the randomized placebo-controlled trials of atypical antipsychotics in bipolar disorder and recent meta-analyses of these agents in acute mania.

2.2 Clinical Studies in Acute Mania

Table 1 provides a summary of randomized placebo-controlled trials of atypical antipsychotics in acute mania, when used either as monotherapy or adjunctive therapy to mood stabilizers. Aripiprazole, asenapine, olanzapine, quetiapine, and risperidone have demonstrated efficacy and got health authority approval in the

Table 1 Atypical antipsychotics in the treatment of acute mania: placebo-controlled, randomized monotherapy, and adjunctive therapy studies

Atypical antipsychotic	Study	Comparator	*N*	YMRS Baseline	YMRS Change from Baseline	*P*-value vs. placebo
Monotherapy trials						
Aripiprazole	Keck et al. (2007)	Aripiprazole	123	28.2	−8.2	0.002
		Placebo	122	29.7	−3.4	
	Sachs et al. (2006)	Aripiprazole	137	28.8	−12.5	≤0.001
		Placebo	135	28.5	−7.2	
	McQuade et al. (2003)	Aripiprazole	129	27.8	−10.8	NS
		Aripiprazole	127	27.9	−10.0	NS
		Placebo	130	28.3	−10.1	
Asenapine	McIntyre et al. (2010)	Asenapine	189	28.3	−10.8	≤0.0001
		Olanzapine	188	28.6	−12.6	≤0.0001
		Placebo	103	29.0	−5.5	
	McIntyre et al. (2009)	Asenapine	183	29.4	−11.5	≤0.01
		Olanzapine	203	29.7	−14.6	≤0.0001
		Placebo	94	28.3	−7.0	
Olanzapine	Tohen et al. (1999)	Olanzapine	50	28.66	−10.3	0.02
		Placebo	66	27.65	−4.9	
	Tohen et al. (2000)	Olanzapine	54	28.76	−14.8	<0.001
		Placebo	56	29.43	−8.1	
Paliperidone	Vieta et al. (2010)	Paliperidone	195	27	−13.2	<0.001
		Quetiapine	193	28	−11.7	<0.001
		Placebo	106	27	−7.4	
Quetiapine	McIntyre et al. (2005)	Quetiapine	101	34	−12.3	≤0.01
		Haldol	98	32.3	−15.7	≤0.001
		Placebo	100	33.1	−8.3	
	Bowden et al. (2005)	Quetiapine	107	32.7	−14.6	<0.001
		Lithium	98	33.3	−15.2	<0.001
		Placebo	95	34	−6.7	
Risperidone	Hirschfeld et al. (2004)	Risperidone	127	29.1	−10.6	<0.001
		Placebo	119	29.2	−4.8	
	Khanna et al. (2005)	Risperidone	146	37.1	−22.7	<0.001
		Placebo	144	37.5	−10.5	
	Smulevich et al. (2005)	Risperidone	153	32.1	−15.1	<0.001
		Haloperidol	144	31.3	−13.9	<0.001
		Placebo	138	31.5	−9.4	
Ziprasidone	Keck et al. (2003)	Ziprasidone	131	27	−12.4	<0.001
		Placebo	66	26	−7.8	
	Potkin et al. (2005)	Ziprasidone	137	26.19	−11.1	<0.01
		Placebo	65	26.42	−5.6	
Adjunctive therapy trials						
Aripiprazole[a]	Vieta et al. (2008a, b)	Aripiprazole	253	23.2	−13.3	0.01
		Placebo	131	23.0	−10.7	
Asenapine	Calabrese et al. (2010)	Asenapine	155		−9.7	≤0.05
		Placebo	163		−7.7	

(continued)

Table 1 (continued)

Atypical antipsychotic	Study	Comparator	*N*	YMRS Baseline	YMRS Change from Baseline	*P*-value vs. placebo
Olanzapine[a]	Tohen et al. (2002)	Olanzapine	220	23.31	−13.1	0.003
		Placebo	114	22.67	−9.1	
Paliperidone	Berwaerts et al. (2011)	Palperidone	150	27	−14.3	NS (0.16)
		Placebo	150	27	−13.2	
Quetiapine	Mullen et al. (2003)	Quetiapine	104	NA	−16.5	NS
		Placebo	96	NA	−14.3	
	Sachs et al. (2004)	Quetiapine	81	31.5	−13.8	0.021
		Placebo	89	31.1	−9.9	
Risperidone	Sachs et al. (2002)	Risperidone	51	28	−14.3	0.009
		Haloperidol	50	27.3	−13.4	<0.003
		Placebo	47	28	−8.2	
	Yatham et al. (2003)	Risperidone	69	29.3	−19.5	NS (0.377)
		Placebo	73	28.3	−17.1	
Ziprasidone[b]	Weisler et al. (2003)	Ziprasidone	99	NA	−0.7	NS
		Placebo	99	NA	−0.7	

YMRS Young mania rating scale
Adapted from Perlis et al. (2006)
[a]All studies or primary endpoints at 3 weeks with the exception of Tohen et al. (4 weeks) and Vieta et al. (6 weeks)
[b]Studies of ziprasidone used the Mania Rating Scale

United States (US) and Europe (EU) for use in acutely manic adults with and without psychosis, as either mono- or adjunctive therapy. All adjunctive trials included subjects who had inadequate response to current treatment with a mood stabilizer, although the study of quetiapine also included subjects who may not have received an adequate course of treatment with lithium or valproate prior to randomization (Sachs et al. 2004). Ziprasidone has demonstrated efficacy and got approved US and EU indications as a monotherapy for acute mania (Bowden et al. 2010). Most pivotal trials of atypical antipsychotics in acute mania included subjects with mixed episodes (with the exception of quetiapine) (Bowden et al. 2005). However, only aripiprazole, olanzapine, and risperidone have been studied in subjects with rapid-cycling bipolar disorder (Zupancic 2011). Aripiprazole, olanzapine, quetiapine, and risperidone have demonstrated efficacy and safety in children and adolescents and are indicated for the treatment of acute mania in pediatric bipolar disorder (Chang 2008; Fraguas et al. 2010; Scheffer et al. 2011).

Few studies exist that directly compare the efficacy of the various atypical antipsychotics in acute mania. Perlis and coworkers conducted a meta-analysis of randomized placebo-controlled, mono- and adjunctive therapy trials of atypical antipsychotics published through 2004 (Perlis et al. 2006). Little difference between agents was observed in efficacy scores versus placebo or in differential response rates among the individual atypical antipsychotics whether used alone or adjunctive to a mood stabilizer. The three monotherapy studies that included active

comparators suggest that atypical antipsychotics had similar efficacy scores compared to lithium and haloperidol, a typical antipsychotic (Yildiz et al. 2011). As expected, the meta-analysis confirmed that adjunctive therapy with an atypical antipsychotic provides additional benefit over monotherapy with a mood stabilizer. Another meta-analysis suggests that antipsychotics are more effective than anticonvulsants when used as monotherapy (Cipriani et al. 2011). However, the relevant question of whether the combination of atypical antipsychotic and mood stabilizer is clinically superior to atypical antipsychotic alone remains unanswered. Nonetheless there appears to be a clear role for atypical antipsychotics in the treatment of acute mania, with a large body of data giving clinicians evidence for use as monotherapy or in combination with a mood stabilizer, in patients with pure and mixed mania, and in those with and without psychosis.

2.3 Clinical Studies in Acute Agitation

Intramuscular (IM) formulations of both aripiprazole and olanzapine are approved for the acute treatment of agitation associated with manic or mixed episodes of bipolar I disorder. In a placebo-controlled study of 291 agitated inpatients with manic or mixed episodes, both 9.75 and 15 mg doses of IM aripiprazole were superior to placebo in reducing acute agitation 2 h post-dose, as measured by the PANSS Excited Component (PEC). Likewise, 10 mg of IM olanzapine was superior to placebo in reducing the PEC 2 h post-dose in a study of 201 acutely agitated inpatients with a manic or mixed episode (Wagstaff et al. 2005). The efficacy for the two appears to be similar (Kinon et al. 2008).

2.4 Clinical Studies in Acute Treatment of Bipolar Depression

Table 2 summarizes the placebo-controlled, randomized monotherapy and adjunctive therapy studies of atypical antipsychotics in the acute treatment of bipolar depression. Quetiapine is the only atypical antipsychotic indicated as a monotherapy for treatment of acute bipolar depression, with efficacy demonstrated in a population of bipolar I and II subjects (Thase et al. 2006). Little is known whether other atypical antipsychotics would be effective as monotherapy in bipolar depression, though two studies of aripiprazole in this population were negative. The combination of olanzapine and fluoxetine is also approved for the acute bipolar I depression. While olanzapine monotherapy did show superiority over placebo, the magnitude of antidepressant effect was greatest with the olanzapine–fluoxetine combination (Tohen et al. 2003). Additionally, an open-label follow-up study of olanzapine–fluoxetine combination showed little risk of inducing mania (Corya et al. 2006).

Table 2 Atypical antipsychotics in the treatment of bipolar depression: placebo-controlled, randomized monotherapy, and adjunctive therapy studies

Atypical antipsychotic	Study	Comparator	*N*	MADRS baseline	MADRS change from baseline	*P*-value vs. placebo
Monotherapy trials						
Aripiprazole	Thase et al. (2008)	Aripiprazole	177	29.1	−12.0	NS
		Placebo	164	28.5	−11.4	
	Thase et al. (2008)	Aripiprazole	176	29.56	−12.3	NS
		Placebo	178	29.35	−11.8	
Quetiapine	Calabrese et al. (2005a, b)	Quetiapine (300 mg)	170	30.3	−16.7	<0.001
		Quetiapine (600 mg)	172	30.4	−16.4	<0.001
		Placebo	169	30.6	−10.3	
	Thase et al. (2006)	Quetiapine (300 mg)	155	29.9	−16.0	<0.001
		Quetiapine (600 mg)	161	31.1	−16.9	<0.001
		Placebo	151	29.6	−11.9	
Combination therapy trials						
Olanzapine-fluoxetine combination (OFC)	Tohen et al. (2003)	OFC	86	30.8	−18.5	<0.001
		Olanzapine	370	32.6	−15.0	0.002
		Placebo	377	31.3	−11.9	

MADRS Montgomery-Asberg depression rating scale
Adapted from Cruz et al. (2009)

2.5 *Clinical Studies in Maintenance Treatment of Bipolar Disorder*

Table 3 summarizes the randomized placebo-controlled trials of atypical antipsychotics as maintenance therapy in bipolar I disorder. Aripiprazole and long-acting risperidone have shown efficacy in the maintenance treatment of bipolar I disorder as mono- and adjunctive therapy (Popovic et al. 2010; Rybakowski 2005; Smith et al. 2007). Olanzapine has proven efficacy as a monotherapy in preventing mood episodes (Weisler et al. 2010), whereas quetiapine and ziprasidone have only been shown to prevent such relapses when given in combination with a mood stabilizer (Vieta et al. 2011).

Although the study designs differed among the pivotal trials for the various atypical antipsychotics, all trials employed a randomized discontinuation after a period of stabilization. While studies of all of the agents included subjects stabilized from an acute manic or mixed state, maintenance studies of quetiapine also included subjects stabilized from acute depressive episodes. The adjunctive study of long-acting injectable risperidone also enrolled euthymic patients and patients stabilized from hypomanic and depressed states.

Table 3 Atypical antipsychotics in the maintenance treatment of bipolar disorder: placebo-controlled, randomized monotherapy, and adjunctive therapy studies

Atypical antipsychotic	Study	Treatment regimen	Comparator	*N*	*P* value vs. placebo for time to recurrence	*N* (%) relapsed overall	*N* (%) relapsed manic	*N* (%) relapse depressed
Aripiprazole	Keck et al. (2007)	Monotherapy	Aripiprazole	78	0.005	19 (24.4)	6 (7.7)	9 (11.5)
			Placebo	83		36 (43.4)	19 (22.9)	11 (13.3)
	Marcus et al. (2011)	Adjunctive	Aripiprazole	168	0.014	25 (17)	7 (5)	14 (10)
			Placebo	169		43 (29)	19 (15)	18 (13)
Olanzapine	Tohen et al. (2006)	Monotherapy	Olanzapine	225	<0.001	105 (46.7)	27 (12)	68 (30.8)
			Placebo	136		109 (80.1)	44 (32)	53 (39)
Quetiapine	Vieta et al. (2008a, b)	Adjunctive	Quetiapine	336	<0.001	62 (18.5)	36 (10.7)	26 (7.7)
			Placebo	367		180 (49.0)	96 (26.2)	84 (22.9)
	Suppes et al. (2009)	Adjunctive	Quetiapine	310	<0.001	63 (20.3)	22 (7.1)	41 (13.2)
			Placebo	313		163 (52.1)	61 (19.5)	102 (32.6)
Long-acting injectable risperidone	Quiroz et al. (2010)	Monotherapy	LAI	154	<0.001	42 (27.3)	22 (14.3)	20 (13.0)
			Risperidone	149		76 (51.0)	62 (41.6)	14 (9.4)
			Placebo					
	Macfadden et al. (2009)	Adjunctive	LAI Risperidone	65	0.010	15 (23.1)	5 + 2 mixed (10.8)	8 (12.3)
			Placebo	59		27 (45.8)	12 + 4 mixed (27.1)	11(18.6)
Ziprasidone	Bowden et al. (2010)	Adjunctive	Ziprasidone	127	0.010	25 (19.7)	7 + 2 mixed (7.1)	16 (12.6)
			Placebo	113		36 (32.4)	14 + 6 mixed (17.7)	16 (14.2)

Although data from most maintenance trials of atypical antipsychotics show greater differences between the active treatment and placebo groups in the number of manic relapses compared to the number of depressive relapses, only the long-term study of quetiapine showed a treatment effect of delaying both manic and depressive relapses (Vieta et al. 2008a, b; Weisler et al. 2010). However, it is important to note that these maintenance trials were not designed to conclude that atypical antipsychotics are more effective in preventing mania than depression. In general, these trials were powered to detect a drug–placebo difference only in the total number of relapses. Moreover, most subjects entered the maintenance phase after an acute manic or mixed episode, thereby biasing the outcome towards more manic episodes.

Little data exist on the comparative long-term efficacy of atypical antipsychotic monotherapy versus mood stabilizers in preventing relapses. Olanzapine, however, has been compared to both lithium and valproate in two separate randomized controlled trials (Suppes et al. 2005a, b; Tohen et al. 2005). Both of these studies showed similar rates of *overall* relapses in subjects receiving olanzapine and each of the mood stabilizers; however, olanzapine appeared to be more effective than lithium in preventing *manic* relapses (13.8 % vs. 23.4 %, $p = 0.002$) (Tohen et al. 2005).

2.6 Tolerability and Safety in Clinical Studies

Table 4 summarizes the safety profiles of the various atypical antipsychotics in patients with bipolar disorder. While this newer generation of agents has a lower risk of extrapyramidal side effects, they carry a significant risk of weight gain and other metabolic side effects, such as hyperglycemia and hyperlipidemia. Weight gain may be particularly problematic in the bipolar patient population, especially if it is additive to the weight gain caused by mood stabilizers. Certain agents, such as olanzapine, have an increased potential for weight gain and hyperlipidemia, and these effects may be more pronounced in adolescents compared to adults (olanzapine prescribing information). Additionally, the sedation associated with some atypical antipsychotics may be especially bothersome to patients who are students or are employed.

2.7 Summary of Clinical Data

A relatively large body of evidence now exists to support the efficacy of atypical antipsychotics in various stages of bipolar disorder. As a class, these drugs appear to be effective in the treatment of acute mania. Indeed, several treatment guidelines have recommended atypical antipsychotic monotherapy as a first-line treatment for acute mania (APA 2002; Suppes et al. 2005a, b), and several studies suggest that the

Table 4 Summary of evidenced-based information on the safety of atypical antipsychotics for uses in bipolar disorder

Drug	Risk of ECG alterations	Risk of weight gain	Risk of other metabolic events	Risk of EPS	Risk of increasing serum prolactin levels
Aripiprazole	–	±	–	±	–
Asenapine	–	+	–	±	–
Olanzapine	–	++	++	±	++
Quetiapine	–	++	NA/I	±	–
Risperidone	–	++	NA/I	++	++
Ziprasidone	±	NA/I	NA/I	NA/I	NA/I

EPS extrapyramidal symptoms; *NA/I* no available data or insufficient data; ± indicates that the drug shows a higher risk of inducing the event compared with placebo; + indicates that the drug shows a higher risk of inducing the event when compared with placebo or one active comparator (either first-generation antipsychotic or mood stabilizer); ++ indicates that the drug shows a higher risk of inducing the event when compared with two different active comparators (either first-generation antipsychotics or mood stabilizers); – indicates that the drug shows a risk of inducing the event that is not different to that shown by placebo
Adapted from Gentile (2007)

combination of an atypical antipsychotic plus a mood stabilizer is more effective than a mood stabilizer alone, especially in patients inadequately responsive to mood stabilizers. Yet, it is not clear if an antipsychotic adjunctive to a mood stabilizer is superior to an antipsychotic alone. Intramuscular formulations of certain atypical antipsychotics are effective in the treatment of acute agitation associated with mania (Kinon et al. 2008; Tran-Johnson et al. 2007). Quetiapine is the only antipsychotic monotherapy to demonstrate efficacy in acute bipolar depression, whereas olanzapine in combination with fluoxetine appears to be effective in bipolar depression with little risk of inducing mania (Benyamina and Samalin 2012). Either of these treatments may have utility in acutely depressed patients requiring rapid treatment response. Most of the atypical antipsychotics have demonstrated the ability to prevent relapse of a mood episode after stabilization from a manic or mixed state, with clear benefit in preventing manic relapses.

The decision to use an atypical antipsychotic in a patient with bipolar disorder, as well as the selection of a particular agent, will depend on factors other than efficacy alone, such as safety, tolerability, compliance, and cost (Perlis et al. 2006). The atypical antipsychotics carry the risk of weight gain and metabolic abnormalities, sedation, and other side effects, some of which may be compounded when used in combination with mood stabilizers. Long-acting injectable risperidone may be a particularly valuable treatment option for bipolar patients with a history of poor medication compliance (Walburn et al. 2001). While pharmacoeconomic factors may also play a role in treatment selection, there are now several generic atypical antipsychotics available.

Further comparative effectiveness trials of atypical antipsychotics are still needed to best evaluate the full utility and value of these agents in clinical practice. Specifically, more data are needed to determine the relative acute efficacy of atypical antipsychotic versus mood stabilizer monotherapy, as well as atypical

antipsychotic monotherapy versus atypical antipsychotic plus a mood stabilizer. Moreover, far fewer agents have demonstrated efficacy for preventing depressive relapse and additional research is needed to establish effective treatments for this phase of the illness.

Atypical antipsychotics have broadened the pharmacological armamentarium for the treatment of bipolar disorder. Furthermore, the exploration of the molecular mechanisms of antipsychotics has helped to shed greater light on the underlying neurobiology of the condition. The subsequent section of this chapter reviews the putative pharmacological mechanisms of antipsychotics, including their effect on monoaminergic neurotransmitters and signaling cascades implicated in the control of neuroplasticity, and cellular resilience.

3 Mechanisms of Antipsychotics in the Treatment of Bipolar Disorder

3.1 Introduction to Mechanisms of Action

As described above, many antipsychotics have been shown to have an antimanic effect, and some of the atypical antipsychotics have also been shown to have antidepressant effects as monotherapy (e.g., quetiapine) or as an adjunct to an antidepressant (e.g., aripiprazole and olanzapine). The primary mechanism of action of antipsychotics is via blockade of dopamine D_2 receptors. Atypical antipsychotics also block serotonin 5-HT_2 receptors and may restore the dampened firing rate of norepinephrine (NE) neurons produced by selective 5-HT reuptake inhibitors, thereby enhancing their antidepressant activity (Blier and Blondeau 2011). In addition, antipsychotics have differing activity on α-adrenoceptors, muscarinic receptors, and histamine receptors. Beyond their effects on neurotransmission, atypical antipsychotics alter intracellular signal transduction and exhibit neuroprotective properties that are mediated by upregulation of trophic and cellular resilience factors.

3.2 Role of Dopamine

The role of dopamine in bipolar disorder has been reviewed extensively (Berk et al. 2007; Cousins et al. 2009; Goodwin 2007; Kapur and Mann 1992). In summary, dopaminergic pathways have been implicated in the core symptoms of bipolar disorders. Historically, dopaminergic models of bipolar disorder were simplistic, dichotomous models suggesting mania as a hyperdopaminergic state and depression as a hypodopaminergic state. However, such a model fails to explain the complexity of the illness and various symptoms or comorbid conditions

(e.g., psychotic symptoms during bipolar depression episodes or attentional deficits during manic episodes). Nonetheless, studies of regional dopaminergic pathways and cell signaling pathways have provided some insight into the pathophysiology of bipolar disorder, as these pathways subserve many of the physical and psychological processes known to be altered in this condition.

Bipolar disorder is a highly heritable illness. Genes encoding the dopamine transporter (DAT), SLC6A3, and rs27072 (Kato 2007; Pinsonneault et al. 2011) have been implicated bipolar disorder, although not consistently (Sklar et al. 2011). Brain imaging studies have not consistently shown any direct evidence of increased or reduced dopaminergic activity, dopamine transporter (DAT) activity, or striatal D_2 dopamine receptor binding in bipolar disorder (Pearlson et al. 1995). Interpretation of neuroimaging findings of the dopaminergic system in bipolar illness is hampered by the fact that subjects were assessed during different phases of illness, bipolar depression, mania or during a euthymic state, as well as while medicated and drug-free in the few studies conducted (Nikolaus et al. 2009).

Dopaminergic psychostimulants, such as amphetamine and methylphenidate, can lead to euphoria or can mimic hypomania. High doses, particularly when taken repeatedly, can cause a number of symptoms including alterations in drive, motivation, impulsivity, and sleep, as well as a full manic episode. Interestingly, these symptoms can be attenuated with treatment with antipsychotics, lithium, or valproate (Berk et al. 2007; Kapur and Mann 1992). Lithium and valproate at therapeutically relevant concentrations have been shown to modulate dopaminergic activity by attenuating the downstream pathways activated by dopamine receptors as shown by studies using forskolin-raised cAMP concentrations which were inhibited by lithium, valproate, and carbamazepine, both in vitro and in vivo (Montezinho et al. 2006). Data from pharmacological interventions support the role of dopamine in bipolar disorder, with most of the antipsychotics having shown antimanic activity (reviewed above).

3.3 Role of Serotonin and Norepinephrine

As discussed above, a few atypical antipsychotics have been shown to improve depressive symptoms. In addition to their affinity to D_2 receptors, atypical antipsychotics are also characterized by their affinity for 5-HT_{2A} and 5-HT_{2C} receptors and effects on norepinephrine (NE) transmission. Potent α_2-adrenergic antagonist activity has been reported for aripiprazole, quetiapine, risperidone, and paliperidone. Blier and others have proposed that blockade of these autoreceptors on the cell body of NE neurons and their terminals can lead to enhanced NE neurotransmission. This effect may be seen especially with norquetiapine, an active metabolite of quetiapine, potentially conferring antidepressant effects while the D_2 blockade may prevent a switch to mania (Blier and Blondeau 2011; Jensen et al. 2008; McIntyre et al. 2009; Prieto et al. 2010).

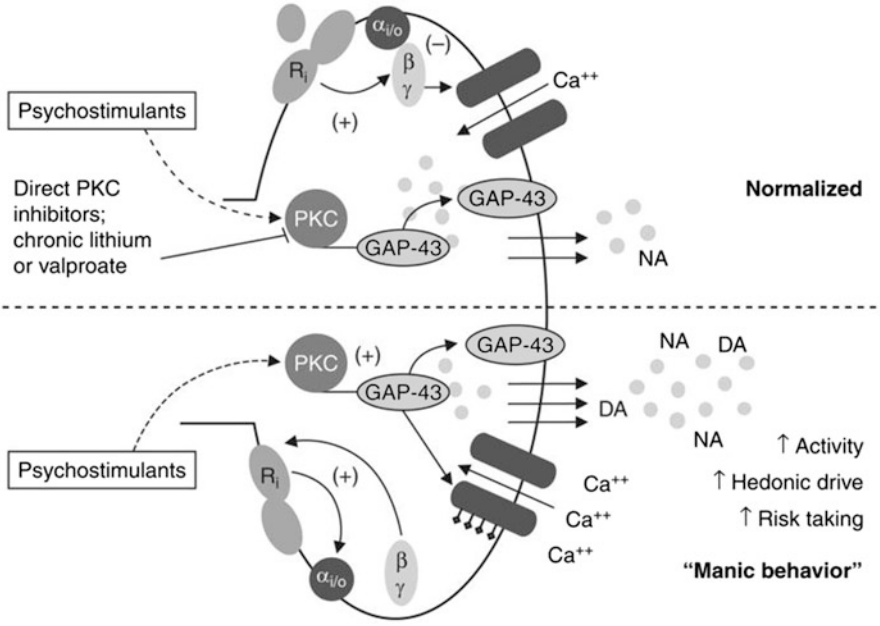

Fig. 1 Protein kinase C (PKC) in the pathophysiology and treatment of manic behavior. *DA* dopamine; *GAP-43* growth-associated protein of 43 kDa; *NA* noradrenaline (norepinephrine); ↑ indicates increased. Figure adapted from Zarate and Manji (2009)

3.4 Signal Transduction Pathways

Activation or blockade of dopaminergic receptors results in changes in intracellular signal transduction leading to alterations in neuronal activity and gene expression. Protein kinase C (PKC) has generated considerable interest as a common target for mood stabilization. Lithium has been shown to act directly on pathways involving phospholipase2 (PLA2), and lithium and valproate on PKC pathways (Fig. 1) (Zarate and Manji 2009). Based upon this hypothesis that PKC is a common target, a number of studies have demonstrated the potential involvement of PKC in the pathophysiology and treatment of bipolar disorder (reviewed in Zarate and Manji 2009). Most critically a number of small proof of concept studies with tamoxifen, a PKC inhibitor, demonstrated a fast onset of efficacy in acute mania (Amrollahi et al. 2011; Yildiz et al. 2008; Zarate et al. 2007), thus corroborating the PKC hypothesis of mania. Although tamoxifen also has antiestrogenic effects, studies with other antiestrogen compounds such as medroxyprogesterone or clomiphene did not attenuate the amphetamine-induced behavioral changes in an animal model of mania that are attenuated by tamoxifen, suggesting that the antiestrogenic effect of tamoxifen is unlikely to contribute to its antimanic property (Pereira et al. 2011). Chronic administration of clozapine and haloperidol has previously been shown to reduce PKC activity in discrete brain areas, e.g., the hippocampus (Dwivedi and

Pandey 1999), which may be relevant for the mechanism of antipsychotic drugs and may in part play a role in the antimanic activity of antipsychotics mediated through PKC inhibition (Zarate and Manji 2009). A recent meta-analysis of the efficacy of antimanic agents supports a larger effect size of tamoxifen compared to antipsychotics (Yildiz et al. 2011). These data add support to the relevance of PKC as a target in bipolar disorder and warrants further studies (DiazGranados and Zarate 2008; Zarate and Manji 2009).

3.4.1 Akt/GSK-3 and Wnt Pathway

Akt is a protein kinase (also known as protein kinase B) that is involved in multiple cellular functions including metabolism, cell stress, cell-cycle regulation, and apoptosis. Akt has a basic role in regulating neuronal cell size and survival (Freyberg et al. 2010). Regulation of Akt by phosphorylated phosphatidylinositol has been associated with the action of insulin, insulin-related peptides (e.g., insulin-like growth factor), and neurotrophins (e.g., nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and neurotrophin (NT)-3) that exert their biological function by stimulating receptor tyrosine kinase (Beaulieu and Gainetdinov 2011). Activation of Akt via phosphorylation by the intracellular kinases PDK1 (3-phosphoinoitide-dependent protein kinase 1) and rictor-mTORC2 (mammalian target of rapamycin complex 2) leads to phosphorylation of other molecules including GSK-3, which plays a significant role in glucose metabolism and in differentiation and development, intracellular trafficking, modulation of synaptic plasticity, apoptosis, and regulation of gene transcription.

In addition to the Akt/GSK-3 pathway, signaling through the Wingless (Wnt) pathway is also of relevance. Wnt proteins are important mediators of cell–cell communication and are involved in diverse cellular processes, including the development of the CNS and play a crucial role in modulation of synaptic plasticity and in neurogenesis and in maintaining and protecting neuronal connections throughout the entire life span (Inestrosa and Arenas 2010). Activated GSK3 promotes β-catenin (a downstream mediator on Wnt signaling) and inhibits protein synthesis. DISC1, one of the most consistently reported risk mutations in schizophrenia and a risk factor for mood disorders (Lipina et al. 2011), regulates adult progenitor cells through GSK-3–β-catenin signaling. Mice lacking DISC1 in the dentate gyrus exhibited schizophrenia-like and depression-like behavior that could be normalized by treatment with a GSK-3 inhibitor (Lipina et al. 2011).

Dopamine-mediated decreases in Akt activity are considered to be mediated by postsynaptic dopamine D_2 receptors. Activation of dopamine D_2 receptor by dopamine or amphetamines leads to recruitment of beta-arrestin 2 and Akt along with the phosphatase PP2A, which dephosphorylates and consequently inactivates Akt, leading to an increase in GSK-3 activity. GSK-3 is constitutively active in resting cells, requiring phosphorylation by kinases such as Akt to inactivate it (Beaulieu et al. 2009). Disruption of Akt's regulation of GSK-3 activity in the brain may also play a role in dysregulation of brain function in schizophrenia and mood disorders (Freyberg et al. 2010).

There is increasing evidence that Akt and GSK-3-related intracellular signaling may at least partially be responsible for the ability of antipsychotic medications to treat symptoms of psychosis and may be a common mechanism for antipsychotics, mood stabilizers, and antidepressants. Some atypical antipsychotics (e.g., clozapine, risperidone, olanzapine, aripiprazole) and typical antipsychotics (e.g., haloperidol) have been shown to either activate Akt or mimic Akt activity by increasing the phosphorylation of its substrates GSK-3 (Roh et al. 2007). However, differences between haloperidol and atypical antipsychotics have emerged in the kinetics of Akt/GSK-3 phosphorylation, the levels of proteins expressed following drug exposure, and the pathway that is preferentially activated (i.e., Akt vs. Wnt pathway signaling) (Roh et al. 2007). Treatment with either haloperidol or clozapine led to phosphorylation of GSK-3α and GSK-3β in rat frontal cortex (Roh et al. 2007). However, whereas levels of phosphorylated Akt1 returned to baseline within 1 hour following acute haloperidol exposure, Akt remained phosphorylated after a similar acute clozapine treatment. The prolonged duration of the effect of clozapine on Akt relative to a typical antipsychotic such as haloperidol may account for its greater effect on downstream molecules in the Wnt pathway (Sutton and Rushlow 2011). In addition, GSK-3 activity is regulated by 5-HT neurotransmission, through the activation of 5-HT_{2A} receptors. It is therefore possible that atypical antipsychotics, which are antagonists of dopamine D_2 receptors and serotonin 5-HT_{2A} receptors, might inhibit GSK-3 activity by acting on dopamine and 5-HT receptor functions (Beaulieu et al. 2007).

Lithium exerts some of its biochemical and behavioral effects by interfering with a β-arrestin signaling complex involved in the regulation of Akt and GSK-3. Lithium's effects on circadian rhythms and mood stabilization have been suggested to be mediated through direct inhibition of GSK-3 at therapeutically relevant concentrations (Gould et al. 2006). Valproate and lamotrigine (but not carbamazepine) have also been shown to indirectly inhibit GSK-3, and this mechanism has been demonstrated by various techniques to result in mood stabilizer-like behavior in rodent models (Gould et al. 2006, O'Brien and Klein 2007). The action of SSRIs and other 5-HT-related antidepressants on GSK-3 as well as the apparent antidepressant-like action of GSK-3 inhibitors in behavioral tests are strongly suggestive of an involvement of GSK-3 in the effects of antidepressants. In summary, in both animal models and the clinical population, GSK-3 manipulation appears to have antidepressant, antipsychotic, and antimanic effects.

Downstream targets of Akt and/or GSK-3 in the action of psychotropic drugs need to be identified and investigated. Whether the role of the Akt/GSK-3/Wnt signaling cascade in mediating behavioral outcomes and actions of psychotropic drugs is confined to certain brain areas is of interest to explore. Interestingly the $mGlu_{2/3}$ agonist, LY379268, which has demonstrated preliminarily clinical antipsychotic efficacy, has also been shown to target Akt and Wnt signaling (Sutton and Rushlow 2011). It is tempting to speculate that this pathway may play a pivotal role in the therapeutic action of antipsychotics.

3.4.2 Neurotrophic Signaling Cascades

Neurotrophins (NTs), a family of peptide growth factors for nerve and glial cells, influence cell cycle, growth, differentiation and survival of neurons and thereby regulate synaptic plasticity in the adult brain. Members of the NT family include NGF, BDNF, NT-3, NT-4, NT-5, and NT-6. BDNF and other neurotrophic factors are necessary for the survival and function of neurons; thus, sustained reductions of these factors could affect neuronal viability.

Endogenous neurotrophic factors have traditionally been viewed as increasing cell survival by providing necessary trophic support. However, it is now clear that their survival-promoting effects are mediated largely by inhibiting cell death (apoptosis) cascades (Lee et al. 2001). Increasing evidence suggests that neurotrophic factors inhibit cell death cascades by activating the extracellular-regulated kinase (ERK) signaling pathway [cyclic adenosine monophosphate (cAMP) response element binding (CREB) is directly phosphorylated and activated by phospho-ERK1/2], the phospholipase C (PLC) cascade, and the phosphoinositide 3-kinase (PI3K)/Akt pathway.

Atypical antipsychotic drugs have been shown to exhibit neuroprotective properties that are mediated by upregulation of trophic factors (Lieberman et al. 2008). Quetiapine reverses the stress-induced decrease in hippocampal BDNF (Fumagalli et al. 2004) and prolongs neuronal survival similar to that shown with antidepressants. Quetiapine and olanzapine have been shown to elicit trophic effects in cultured neuronal cells by activation of Akt and ERK, which could indicate mitogenic and neuroprotective effects (Di Benedetto et al. 2011). Although antidepressants and antipsychotics both increase neurogenesis, the effect of antidepressants is restricted mainly to the subgranular zone (SGZ) of the dentate gyrus, with no impact on subventricular zone (SVZ) of the lateral ventricles in the forebrain (Samuels and Hen 2011). However, antipsychotic drugs have been reported to promote neurogenesis in both the SGZ and SVZ (Newton and Duman 2007). Additionally, haloperidol, a typical antipsychotic drug and potent D_2 receptor antagonist, significantly increases cell proliferation in the SVZ, resulting in new neurons in the olfactory bulb and non-neuronal cells in the striatum (Deutch et al. 1995). The striatal cell proliferation would explain the caudate enlargement (Newton and Duman 2007) that has been reported with long-term administration of typical antipsychotic drugs but not atypical agents. Despite the robust SVZ neurogenesis, antipsychotic drugs with high D_2 receptor specificity do not seem to increase hippocampal proliferation. In contrast, atypical antipsychotic drugs that exhibit affinity for serotonin receptors increase SGZ neurogenesis in addition to non-neuronal proliferation in the frontal cortex (Newton and Duman 2007). Whether atypicals are still able to induce SVZ proliferation is somewhat controversial as some studies report this effect (Green et al. 2006) while others do not (Councill et al. 2006).

The overlap that is seen in proliferation profiles of SSRI antidepressants and atypical antipsychotic drugs, particularly with 5-HT_2 inhibitory activity, is striking

(Nasrallah et al. 2010) but still only correlative, with the precise underlying mechanism remaining unclear. Studies with specific serotonin agonists and antagonists have shed light on some of these mechanisms. The role of D_2 receptors in haloperidol-induced proliferation was addressed by generating D_2 receptor null mice that do not exhibit an increase in neural stem cells with haloperidol administration (Newton and Duman 2007). These data also suggest that dopamine signaling via activation of D_2 receptors has an anti-proliferative effect, which is overcome by the antagonistic effect of haloperidol (Newton and Duman 2007). However, there is still significant controversy regarding the contribution of D_2 receptors, as D_3 receptor activation was earlier shown to stimulate adult SVZ (Merlo et al. 2011) and substantia nigra (Collo et al. 2008) neurogenesis.

3.4.3 The Bcl-2 Family of Proteins

The B-cell lymphoma protein (Bcl-2) family includes pro- (such as Bax and Bad) and anti-apoptotic (such as Bcl-2 and Bcl-xL) proteins (Youle and Strasser 2008). Several preclinical studies have shown that atypical antipsychotics, including olanzapine, risperidone, and quetiapine upregulate levels of Bcl-2 or Bcl-xL in the brain after chronic administration (Hammonds and Shim 2009; He et al. 2004, 2006; Keilhoff et al. 2010; Luo et al. 2004). The mechanism through which atypical antipsychotics upregulate Bcl-2 is still largely unknown. However, Bcl-2 effects of atypical antipsychotics illustrate that atypical antipsychotics and mood stabilizers can produce similar intracellular actions, and this might explain in part the efficacy of atypical antipsychotics in the treatment of mood episodes and in the prevention of recurrence.

These Bcl-2 family proteins are known to play essential roles in apoptosis. They also play non-apoptotic regulatory roles in mitochondrial function, endoplasmic reticulum stress, calcium homeostasis, neurite growth, axonal regeneration, AMPA receptor trafficking and synaptic plasticity (Chen et al. 2010; Hunsberger et al. 2009; Jiao and Li 2011; Jonas 2006, 2009; Kim et al. 2008; Li and Jope 2010; Youle and Strasser 2008). Chen et al. (1999) found that upregulation of Bcl-2 in the brain is a common effect of two structurally distinct mood stabilizers, lithium and valproate. They also determined that the upregulation is at least in part through activation of the ERK MAP kinase (Creson et al. 2009; Einat et al. 2003; Yuan et al. 2001). The ERK activation led to activation of CREB, a transcription factor, and upregulation of bcl-2 gene transcription (Creson et al. 2009; Einat et al. 2003; Yuan et al. 2001). The follow-up studies from their group and others show that mood stabilizers also enhance cellular function of Bcl-2, including neuronal protection against death-inducing insults, neurite and axonal growth, calcium signaling, and mitochondrial function (Chen et al. 2010; Hunsberger et al. 2009; Machado-Vieira et al. 2011). The same group also demonstrated that lithium and valproate upregulated another Bcl-2-related protein, BAG1, and modulated a BAG1 unique function, glucocorticiod receptor translocation to nuclei (Zhou et al. 2005). Their follow-up behavioral studies show that Bcl-2 proteins including Bcl-2, BAG1,

BI-1, and tBid are sufficient to modulate behavioral outcomes in a wide range of rodent models of mood disorders (Chen et al. 2010; Einat et al. 2005; Hunsberger et al. 2011; Lien et al. 2008; Maeng et al. 2008; Malkesman et al. 2011). The paradigms include the forced swim test, tail suspension test, learned helplessness paradigm, anhedonia-like deficits induced by serotonin and catecholamine depletion, amphetamine-induced hyperlocomotion, and amphetamine-induced behavioral sensitization. Human postmortem brain studies reveal lower levels of Bcl-2 (Kim et al. 2010), higher levels of Bax and Bad (Kim et al. 2010), and lower levels of ERK pathway components in cortical tissues from bipolar patients (P. Yuan et al. 2010). These coherent data indicate the possible role of Bcl-2 dysfunction in bipolar disorder. Some studies also revealed lower levels of Bcl-2 (Jarskog et al. 2000); a higher ratio of Bax vs. Bcl-2 (Jarskog et al. 2004), and lower levels of ERK/MAP kinase pathway components in the postmortem brain tissues from schizophrenia patients (Yuan et al. 2010). These data suggest that Bcl-2 dysfunction is a common intracellular arbiter of both illnesses, though the Bcl-2 dysfunction might reside in different neuronal circuitries and/or different cell types in these two different illnesses.

3.5 Summary of Preclinical Studies and Future Directions

A considerable body of evidence supports abnormalities in the regulation of cellular plasticity cascades as an integral part of the neurobiology underlying bipolar disorder. Many of these pathways play critical roles in immediate synaptic plasticity, and in long-term cell growth/atrophy and cell survival/cell death. Indeed, the atrophic changes observed in multiple cell types (neurons and glia), as well as the reversibility of the changes with treatment, support a role for intracellular plasticity cascades. It is likely that the major defect is in the ability to regulate neuroplastic adaptations to perturbations (both physiological and pathophysiological) and the inability to handle "normal loads" (neurochemical, hormonal, stress-induced, pharmacologically induced, etc.) without failing or invoking compensatory adaptations that overshoot and predispose to oscillations.

Antipsychotics appear to affect a number of these targets, underlying their utility in mood disorders. Newer "plasticity enhancing" strategies that may have utility in the treatment of mood disorders include inhibitors of glutamate release, N-methyl-D-aspartate antagonists, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid potentiators, and PKC inhibitors. Indeed, such potential next-generation drugs, in addition to treating the core symptoms of bipolar disorder, might be able to target other important aspects of the illness. These aspects include enhancing cognition independent of any improvement in mood symptoms, and preventing or reversing epigenetic factors that may have long-term negative impacts on the course of the illness. The development of novel therapeutics holds much promise for the long-term treatment of severe mood disorders and for improving the lives of the many who suffer from them.

4 Conclusions

Atypical antipsychotics have an important role in the acute and maintenance treatment of bipolar disorder. While a large body of evidence supports the efficacy of these agents in the various stages of bipolar disorder, more comparative effectiveness studies are needed to assess the optimal treatment regimens, including the relative benefits and risks of antipsychotics versus mood stabilizers. The growing understanding of the underlying neurobiology of bipolar disorder, along with the ability of atypical antipsychotics to target key pathophysiological pathways of this condition, suggests that these medications exert their therapeutic effect through a variety of mechanisms. Further, the development of novel "plasticity-enhancing" therapeutics brings hope for the future treatment of patients with bipolar disorder.

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