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Atypical Depression
A Comprehensive Review

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Contents

Abstract

Despite several decades of research, the characteristics distinguishing atypical depression from other depressive subtypes remain ambiguous. Multiple lines of evidence support the designation of atypical depression as a scientifically and clinically relevant subtype, including differences in hormonal responses, brain laterality, psychological profile and psychiatric co-morbidity and differential treatment response. The evolution of the diagnostic criteria for atypical depression has led to the designation of mood reactivity as the cardinal feature, and the research supporting this conclusion is reviewed.

This paper also reviews the evidence for the drug treatment of atypical depression, with a particular focus on research related to the superior efficacy of monoamine oxidase inhibitors (MAOIs) compared with tricyclic antidepressants (TCAs). Data relevant to the efficacy of newer antidepressants, including selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline (norepinephrine) reuptake inhibitors, transdermal selegiline and other new agents for atypical depression, are discussed.

In summary, the diagnostic reliability and validity of atypical depression still remain elusive and open to further evolution. Currently available findings suggest that atypical depression has preferential response to MAOIs over TCAs. More data are required to determine the efficacy of newer agents relative to MAOIs and TCAs, although limited studies have shown a non-inferior efficacy and better tolerability of newer agents such as SSRIs compared with those of MAOIs and TCAs. Finally, future directions for research include further refinement of the diagnostic criteria for atypical depression, and clarification of the role of newer antidepressants in the treatment of this subtype with evidence from randomized, controlled trials.

Atypical depression is a subtype of depression that the DSM-IV defines as having the characteristics of reactive mood (including the ability to respond emotionally to environmental cues), increased appetite, hypersomnia, leaden paralysis and interpersonal rejection sensitivity.[1] 'Depression with atypical features' (or atypical depression) is the term used for a depressive episode with the above characteristics during the course of a longitudinal mood disorder (i.e. major depressive disorder [MDD], dysthymic disorder, or bipolar I and II disorders). It is important to note that the atypical features specifier is applied only once the DSM criteria for the longitudinal disorder are met, such that satisfying the criteria for the atypical features specifier alone is not sufficient to diagnose a patient with atypical depression.[1] According to the atypical features specifier, mood reactivity and two or more of the other features must predominate in the most recent 2-week period of a major depressive episode of major depression or bipolar I or II disorders or be present during the most recent 2 years of dysthymic disorder for the depressive episode to be considered atypical depression.[1] Literature describing the characteristics of atypical depression has been fairly consistent since the term's first inception, although terms used to describe the absence of atypical features have varied in studies. Depressive episodes that do not fulfil criteria for atypical features have been variously described as 'typical', 'nonatypical', 'endogenous' (implying biochemical etiology) and 'melancholic' (usually referring to meeting DSM criteria for melancholic features).[2] The current article uses the term 'typical' rather than the other terms used in literature for depressive disorder.

We identified relevant studies through a PubMed literature search (January 1980–December 2008) with a combination of the following search terms: 'atypical', 'depression', 'epidemiology' (e.g. prevalence), 'etiology' (e.g. neurobiology, neurotransmitter and genetic), 'diagnosis' and 'treatment' (e.g. antidepressant with a specific name). In addition, studies were identified through references of retrieved articles. Findings were then synthesized by the categorical themes. We thoroughly reviewed major findings from the identified literature and offer a summary, along with interpretations and opinions regarding future research directions.

Our article describes and discusses the history, concept and clinical features of atypical depression. We focus on the currently available pharmacological treatment options for atypical depression, including innovations over several decades, such as selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline (norepinephrine) reuptake inhibitors (SNRIs), novel antidepressant classes and the recent introduction of the safer monoamine oxidase inhibitor (MAOI), transdermal selegiline (deprenyl).

1. Epidemiology

Individuals with atypical depressive episodes are 2- to 3-fold more likely to be women and often have a more chronic, unrelenting course of depression than individuals with typical depression.[1] Patients with atypical depressive episodes generally have a younger mean age of onset.[3-7] In addition, a high concordance of atypical depression has been observed in monozygotic twin

pairs, indicating a possible genetic component in the disorder.[8] Studies have shown no significant differences between atypical and typical major depression patients with regard to demographic features such as race, ethnicity, employment status, family history of depression or years of education.[5,6,9]

Rates of atypical depression in a study of the general population in Zurich, Switzerland were 4.5% for women and 1.2% for men, with atypical depression being 4-fold less prevalent in the population overall than typical depression.[6] Studies of community samples have shown that 15–29% of patients with MDD have atypical depression, which means a 1-year prevalence of approximately 1–4% (see review by Thase[10]). On the other hand, studies of clinical populations have shown remarkably similar estimates, with 18–36% of patients with MDD presenting with atypical depression (see review by Thase[10]).

The atypical depression lifetime prevalence rate in another study has been estimated to be 0.7%.[4] In a sample of 243 outpatients with depression, 35.8% had atypical depression.[11] In a study of outpatients with MDD, 20.8% of the women and 13.7% of the men had atypical depression.[12] In a sample of 8116 individuals aged 15–64 years, 17.1% of the patients with a diagnosis of major depression had a history of atypical depression.[13] Of 1500 outpatients studied in the STAR*D (Sequenced Treatment Alternatives to Relieve Depression) trial, 18.1% of patients in the trial had depression with atypical features, and women were 70% more likely to have atypical depression.[5] In another study with 114 depressed outpatients, 29% of them exhibited atypical depression, with 87.9% of the patients with atypical depression being female.[14] Of 1000 consecutive admissions to an outpatient psychiatric clinic, 15% of patients with major depression met the Columbia criteria[15] for definite atypical depression (see section 3), and at least 10% of all the participants in the study had atypical depression.[9]

2. Psychobiological Hypotheses

Although atypical depression is common and well characterized in DSM-IV, little is known about its biological and psychological mechanisms.

2.1 Biological Hypothesis

2.1.1 Hormonal Axis

One relevant study in depressed patients compared the cortisol response to desipramine, a relatively selective noradrenaline reuptake inhibitor, in a group meeting full criteria for atypical features with the cortisol responses in a group with no atypical symptoms and a group with mood reactivity as the only atypical symptom.[16] The group of patients with atypical depression showed a significantly higher cortisol response than the other two groups, indicating that atypical depression may be associated with less impairment of the noradrenaline neurotransmitter system.[16] Similarly, hypersecretion of corticotropin-releasing hormone (CRH) and resulting hypercortisolism, which is a well documented physiological marker of typical depression, was found to be absent in patients with atypical depression; significantly lower CRH levels were noted in patients with atypical depression than in healthy controls.[17] These findings are also consistent with the observation that MAOIs have been repeatedly found to be more efficacious for treating atypical depression than tricyclic antidepressants (TCAs), which have potent noradrenergic properties. This distinction between MAOIs and TCAs may indicate different biological mechanisms at work in patients with atypical depression.[18,19] In fact, some researchers have suggested that serotonergic neurotransmission is more relevant than noradrenergic transmission to the pathophysiology of atypical depression.[20]

2.1.2 Brain Hemispheric Bias

According to chimeric faces studies,[21] atypical depression and typical depression have a clearly different hemispherical bias in the brain. Patients with atypical depression showed increased right parietal processing, whereas those with typical depression demonstrated increased left parietal processing.[21] The tendency towards scoring in the opposite direction in patients with typical depression, and closer to healthy controls in patients with atypical depression has also been proposed by research of pattern-reversed, visual evoked potentials.[22] Single photon emission CT with 99mTc-hexamethylpropylene amine oxime

indicates differential brain activity in patients with atypical depression compared with typical depression; patients with atypical depression showed an increase in right frontal lobe perfusion, whereas those with typical depression had decreased perfusion in the majority of non-occipital regions.[23]

2.2 Psychological Hypothesis

Personality and temperament characterization have also been conducted in order to discriminate patients with atypical depression from those with typical depression.[24] Parker et al.[2,24] have suggested the arborizing and spectrum model to define atypical depression, converging onto the primacy feature of interpersonal rejection sensitivity, which is accompanied by a variety of dysregulated emotional (overridden anxiety) and self-consolatory (hypersomnia and hyperphagia, etc.) responses. The authors propose that atypical depression may be a spectrum disorder, although this model has not yet been validated.

These findings suggest that atypical depression might be a biologically and psychologically distinct subtype, although further research is indicated to validate this framework.

3. Diagnosis

The history of atypical depression has centred around two points: a good response to MAOI treatment, and features that distinguish atypical depression from classical depression, which is associated with depressed mood, anhedonia, weight loss, insomnia, fatigue, guilt and the inability to concentrate. The studies mentioned below illustrate how different treatment responses and atypical features have been studied over time and how these features were moulded to form the current DSM-IV definition of depression with atypical features.[1]

The idea of atypical depression really started drawing attention when, after giving the first developed MAOI iproniazid to over 500 patients, West and Dally[18] noticed that certain types of depressed patients responded to the medication much more than other depressed patients, even after other therapies had failed. They reported that these atypical patients had more anxiety, phobia, fatigue and trouble falling asleep at night. These patients were not as likely to wake early in the morning (as is often the case with depressed patients) and they also felt worse as the day progressed (reversed diurnal variation), rather than the opposite situation typically seen in depression. By contrast, iproniazid was not as helpful for patients with more typical depression. This helped advance the idea that an atypical depression existed that could be treated in a different manner from typical depression.

In 1960, Sargant[25] published a paper describing atypically depressed patients exhibiting anxiety, emotionality, phobias and hyper-reactivity, who could not be helped by electroconvulsive therapy or other treatments. These patients would sleep well or have trouble falling asleep, but they did not exhibit classic early morning awakening. They also exhibited reversed diurnal variation. As before, these patients responded very well to iproniazid, which could sometimes even prevent recurrent bouts of depression in patients who were unable to prevent recurrence through other treatment options.

Although the previously mentioned studies were clear in their findings, they were based more on clinical observation than on well designed experiments. More credence was given to the idea that atypically depressed patients responded better to MAOIs after a double-blind, placebo-controlled study showed the efficacy of the MAOI phenelzine in the treatment of atypical depression.[26] A subsequent study went so far as to suggest that MAOIs be used as first-line therapy for atypical depression, although some doubt still centred on the exact definition of atypical depression.[27]

A review of past studies relating to atypical depression described the great breadth of symptoms that had been associated with atypical depression up to that point, notably anxiety, increased appetite, weight gain, hypersomnia, early stage of onset, higher prevalence in women, good response to MAOIs, paranoia, obsession, mood lability and irritability, among others.[28] The article pointed out the wide variety of symptoms that had been

associated with atypical depression and called for a more concrete operational definition to further advance the study and treatment of this type of depression.

In 1988, Quitkin et al.[29] at Columbia University in the US called for a separate DSM category for atypical depression on the basis of their study, which showed that patients meeting their self-developed definition of atypical depression (reactive mood and two or more of the four associated symptoms of hyperphagia, hypersomnia, leaden feeling and sensitivity to interpersonal rejection) or probable atypical depression (reactive mood and one associated symptom) benefited more from the MAOI phenelzine than from the TCA imipramine. At this point the characteristics of patients who responded preferentially to MAOIs were becoming defined in more concrete terms. This definition of atypical depression, known as the Columbia criteria, was for the most part adopted in the current DSM-IV-R definition of depression with atypical features.[1]

It should also be noted that the required feature of reactive mood in atypical depression has been questioned in the last few years because of a lack of a correlation of mood reactivity with the four accessory symptoms of atypical depression (significant weight gain or increase in appetite, hypersomnia, leaden paralysis and long-standing pattern of interpersonal rejection sensitivity).[30] In addition, there is not a significant correlation between reactive mood and any of the four accessory symptoms individually among depressed patients.[24] This poor correlation of the hallmark symptoms of atypical depression calls into question the assertion that atypical depression is a distinct entity with a set of defining characteristics. Parker[24] has recently argued that atypical depression is really better characterized as a syndrome "whereby individuals with a personality style of interpersonal rejection sensitivity are predisposed to also develop anxiety disorders … (and) respond to their dysphoria through a variety of dysregulated emotional and self-consolatory responses, which may reflect some homeostatic mechanisms (e.g. hypersomnia, hyperphagia) designed to settle the emotional dysregulation." This is an interesting new concept that might better account for the association of anxiety disorders, interpersonal rejection sensitivity, hyperphagia and hypersomnia in atypical depression.

Therefore, the epistemological viewpoint on atypical depression remains inadequate, although several leading research groups have progressed the conceptual understanding for refining the diagnostic criteria of atypical depression. Researchers and clinicians should be open to new perspectives on atypical depression, to enable the establishment of diagnostic reliability and clinical validity for this disorder.

4. Co-Morbidity

It is generally considered that atypical depression has higher rates of co-morbid psychiatric illness than typical depression, although data have been inconsistent. A study of 579 outpatients with MDD suggests higher rates of psychiatric co-morbidity among atypically depressed patients.[30] The percentages of patients with certain co-morbidities in each group (atypical depression patients and typical depression patients) are shown in table I.[30] Similarly, it has been reported that patients with atypical depression are twice as likely to have co-morbid panic disorder or drug abuse or dependence disorders than patients with typical depression.[4] However, in contrast, a study of 1029 female-female twin pairs yielded lower rates of anxiety or panic attacks in those with atypical compared with typical depression.[8] This study demonstrated high lifetime rates of alcoholism (26.3%), phobias (48.8%) and bulimia (19%) in the atypical depression group.[8] A hallmark study of National Comorbidity Survey data associated the atypical subtype of major depression with increased risk of conduct disorder and social phobia, and also demonstrated more frequent interpersonal dependency, low self-esteem and parental history of alcohol/drug use disorder compared with the typical depressive group.[31]

Depressed patients meeting criteria for the related diagnoses of social phobia and avoidant personality disorder may be at particularly high risk of atypical features. One study reported that depressed patients with atypical features are 2.5-fold more likely to meet diagnostic criteria

Table I. Summary of co-morbidity of atypical depression

Study	Co-morbidities	Patients (%)	
		atypical depression	typical depression
Posternak and Zimmerman[30]	Specific phobia	18.5	14.0
	Social phobia	54.6	32.3
	OCD	13.8	12.7
	PTSD	30.8	25.8
	GAD	20.0	15.4
	Hypochondriasis	5.4	1.6
	Bulimia	6.2	2.7
	Body dysmorphic disorder	6.9	1.8
	Drug/alcohol abuse/dependence	41.5	43.2
	Amfetamine abuse	3.8	4.2
Horwath et al.[4]	Panic disorder	14.4	7.2
	Somatization disorder	1.9	0.2
	Simple phobia	28.0	22.0
	Alcohol abuse/dependence	22.0	16.0
	Drug abuse/dependence	28.8	12.0
	Agoraphobia	12.5	14.5
	Social phobia	7.7	5.4
	Dysthymia	43.3	36.0
Alpert et al.[11]	Social phobia	8.1	12.6
	Avoidant PD	11.5	8.1
	Both (social phobia and avoidant PD)	26.4	10.3
	Neither (social phobia or avoidant PD)	54.0	69.0
Angst et al.[6]	Panic disorder	17.0	8.0
	Social phobia	25.0	10.0
	All phobias	37.0	22.0
	GAD	35.0	29.0
	Binge eating	27.0	10.0
	Alcohol abuse/dependence	31.0	29.0
	Drug abuse/dependence	19.0	12.0
	Neurasthenia	54.0	14.0
	Sociopathy	16.0	10.0

GAD = generalized anxiety disorder; **OCD** = obsessive-compulsive disorder; **PD** = personality disorder; **PTSD** = post-traumatic stress disorder.

for both of these disorders than depressed patients without atypical features.[11] A Swiss study of atypical depression patients (with no typical depression comparator group) demonstrated frequent co-morbid generalized anxiety disorder (35%), social phobia (25%) and binge eating (27%).[6]

In an Italian study of 83 patients with atypical depression, 32.6% of the patients with atypical depression had bipolar II disorder, 30% had social phobia, 42% had body dysmorphic disorder, 20% had obsessive-compulsive disorder and 64% had panic disorder.[32] The authors noted that a striking 72% of the atypical depression patients met criteria for bipolar disorder when 'soft' bipolar diagnoses were considered, supporting a widespread belief that atypical depressive episodes are a common presentation of bipolar disorder. A study of depressed outpatients (n = 483) with MDD and bipolar II disorder demonstrates that atypical features are more frequent in bipolar patients (53.7%) than in MDD patients

(27.7%).[3] However, data from a smaller study of 109 depressed patients (79 unipolar and 30 bipolar) showed similar prevalence rates of atypical features among bipolar and unipolar patients (30% and 28%, respectively).[33]

It appears that atypical depression has greater co-morbidity with a variety of anxiety disorders (e.g. social phobia) and other mood disorders (e.g. bipolar disorder), eating disorders and substance-related disorders. Hence, it is prudent for clinicians to consider various co-morbid conditions that may affect clinical outcomes in patients with atypical depression.

5. Pharmacological Treatment

Psychopharmacological dissection refers to the identification and validation of phenomenological subtypes based on differential treatment response to psychiatric medications. In this context, there has been a long-standing interest in characterizing this unique group of depressive patients who preferentially benefit from MAOIs compared with TCAs. The advent of newer antidepressants, including SSRIs and SNRIs, has triggered further exploration through clinical trials.[34]

5.1 Antidepressants

5.1.1 Traditional Antidepressants

Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

In the retrospective analysis by West and Dally[18] described in section 3, the presenting symptoms and response characteristics of 101 consecutive, iproniazid-treated patients were analyzed and reported. Good treatment response was observed in 58 patients exposed to iproniazid (50–150 mg/day). Within this group the investigators found that the most rapid, robust and unexpected responses to iproniazid occurred in a select group of patients with 'atypical or hysterical' depressions characterized by chronic duration of illness, greater extent of phobic anxiety, general inadequacy compared with 'endogenous' depression, prominent somatic symptoms such as hysteria and tremor, over-reactivity, fatigue, lack of classic early morning awakening or diurnal mood variation (or worsening of mood in the evening), lack of self-reproach compared with typical depressive patients, and marked amnestic adverse effects to electroconvulsive therapy.[18] The identification of this symptom cluster as a relevant subtype of depression was supported by a number of studies conducted around that time.[35,36]

Multiple randomized, double-blind, controlled clinical trials to date have demonstrated the efficacy of MAOIs in depression with atypical features,[26,37,38] and the superiority of MAOIs to TCAs in this disorder.[19,29,39-45] The largest of these studies was conducted by Liebowitz et al.[40] as a follow-up to a smaller preliminary study,[39] and included 119 patients who met specific research diagnostic criteria for atypical depression (depression and mood reactivity with two other symptoms such as hypersomnia, overeating, extreme fatigue during depression, or chronic hypersensitivity to rejection). These patients were randomly assigned to treatment with phenelzine, imipramine or placebo for 6 weeks in a double-blind condition.[40] Phenelzine was found to be superior to placebo and demonstrated a trend towards superiority to imipramine, with responder (defined as Clinical Global Impression-Improvement [CGI-I] score ≤2 at the end of the study) rates of 71% in the phenelzine-treated group, 50% in the imipramine-treated group and 28% in the placebo group (table II). The finding of an efficacy advantage in the MAOI group is consistent with previous research indicating that MAOIs have a unique role in treating patients with features now recognized as atypical.[18,35,36] A subsequent replication study of 90 atypical depression patients yielded similar results, with responder (CGI-I score ≤2 at the end of the study) rates of 83% in the phenelzine-treated group, 50% in the imipramine-treated group and 19% in the placebo-treated group.[41]

A finding of interest regarding the phenomenology of atypical depression is that the superiority of phenelzine to imipramine was detected in patients with definite atypical depression (n = 120) defined as reactive mood plus two associated atypical symptoms (out of four possible symptoms: hyperphagia, hypersomnolence,

Table II. Summary of antidepressant trials (with monoamine oxidase inhibitors, tricyclic antidepressants and selective serotonin reuptake inhibitors) for atypical depression

Study (year)	Design	No. of pts	Duration (wk)	Medications	Outcome[a]
Liebowitz et al. (1988)[40]	r, db	119	6	PNZ, IMI, PBO	PNZ 71%, IMI 50%, PBO 28%
Liebowitz et al. (1984)[39]	r, db	60	6	PNZ, IMI, PBO	PNZ 67%, IMI 43%, PBO 29%
Quitkin et al. (1988)[29]	r, db	60	6	PNZ, IMI, PBO	PNZ 71%, IMI 47%, PBO 29%
Quitkin et al. (1990)[41]	r, db	90	6	PNZ, IMI, PBO	PNZ 83%, IMI 50%, PBO 19%
Quitkin et al. (1991)[42]	db, co	64	12	PNZ, IMI	PNZ 63%, IMI 35%
McGrath et al. (1993)[44]	db, co	89	12	PNZ, IMI	PNZ 67%, IMI 41%
Stewart et al. (1997)[46]	r, db	60	24 (after stabilization period of 24 wk treatment with PNZ or IMI)	PNZ, IMI, PBO	PNZ 23%,[b] IMI 41%, switched from IMI to PBO 47%, switched from PNZ to PBO 87%
Jarrett et al. (1999)[47]	r, db	108	10	PNZ, CBT, PBO	PNZ 58%,[c] CBT 58%, PBO 28%
Pande et al. (1996)[43]	r, db	40	6	PNZ, FOX	PNZ 85%, FOX 80%
Larsen et al. (1991)[48]	r, db	167	6	MCB, ICB, CMI	MCB < ICB < CMI
Larsen et al. (1984)[49]	r, db	38	6	MCB, CMI	MCB = CMI
Sogaard et al. (1999)[50]	r, db	197	12	MCB, SERT	MCB 63%, SERT 65%
Lonnqvist et al. (1994)[51]	r, db	53	6	MCB, FOX	MCB 67%, FOX 55%
McGrath et al. (2000)[52]	r, pc	154	10	FOX, IMI, PBO	FOX 51%, IMI 53%, PBO 23%
Stratta et al. (1991)[53]	r, db	28	6	FOX, IMI	FOX = IMI
Joyce et al. (2002)[54]	r, db	195	6	FOX, NTP	FOX 67%,[d] NTP 0%
Pae et al. (2008)[55]	sb	15	8	ECP	67%[e]

a Percentages of patients achieving a ≥50% reduction in Hamilton Depression Rating Scale score and/or achieving a Clinical Global Improvement score ≤2 at the end of trial.

b Recurrence rate.

c Endpoint of Hamilton Depression Rating Scale score ≤9 and Clinical Global Improvement score ≤2.

d ≥60% reduction in Montgomery-Åsberg Depression Rating Scale score.

e ≥50% reduction in Structured Interview Guide for the Hamilton Depression Rating Scale – Seasonal Affective Disorder (SIGH-SAD) total score.

CBT = cognitive behavioural therapy; **CMI** = clomipramine; **co** = crossover; **db** = double-blind; **ECP** = escitalopram; **FOX** = fluoxetine; **ICB** = isocarboxazid; **IMI** = imipramine; **MCB** = moclobemide; **NTP** = nortriptyline; **PBO** = placebo; **pc** = placebo-controlled; **PNZ** = phenelzine; **pts** = patients; **r** = randomized; **sb** = single-blind; **SERT** = sertraline.

leaden feeling and sensitivity to rejection)[19] and also in patients with probable atypical depression (n = 60) defined as reactive mood plus one additional atypical symptom.[29] This provides validation for the consideration of reactive mood as the hallmark feature of atypical depression, and the authors of these two important studies concluded that this treatment response distinction reveals that atypical depression may be a clinically and heuristically useful subtype of depressive disorders.[19,29]

Clinical trials employing crossover design have also demonstrated the efficacy advantage of phenelzine over imipramine in patients who met Columbia University criteria for atypical depression. The first such study randomized the order of treatments (12 weeks in total) in patients failing to respond during a 7-week placebo lead-in.[42] A subsequent trial by the same investigators enrolled atypically depressed patients who were unresponsive to vigorous double-blind trials of imipramine or phenelzine by crossing them over to treatment with the other drug under double-blind conditions.[44] In this uniquely designed study, 31 patients (67%) responded to phenelzine among 46 patients previously unresponsive to imipramine, whereas nine patients (41%) responded to imipramine among 22 patients previously unresponsive to phenelzine. Many of these cited studies were conducted by the same team of

investigators at Columbia University, who used their operational criteria for atypical depression requiring mood reactivity along with at least one additional atypical symptom (i.e. hypersomnia, weight gain, overeating, severe fatigue and unusual sensitivity to rejection). These pivotal clinical trials[19,29,40-42] largely contributed to the establishment of atypical depression as one of the separate depressive episode subtypes in the mood disorders section of the DSM-IV.

The superiority of phenelzine over imipramine in the treatment of atypical depression was supported in a recent meta-analysis that included randomized studies conducted in a double-blind, controlled, fashion and employing operational diagnostic criteria for atypical depression.[56] Results were included from four randomized, controlled clinical trials in patients with atypical depression,[29,40-42] all of which favoured phenelzine over imipramine, showing a mean effect size of 0.27 (range of effect size in the four studies: 0.21–0.35).[56] In the comparison of phenelzine with placebo,[29,40,41,47] the mean effect size was 0.45 (range of effect size in the four studies: 0.31–0.64).[56] Overall, the results of this meta-analysis are in line with previous literature proposing that patients with atypical depression show a better response to MAOIs than to TCAs or placebo.[15] However, the small to medium effect sizes revealed in the meta-analysis[56] indicate that the consistent statistical superiority of phenelzine in research studies may not fully translate into marked advantages in clinical practice.

In a long-term, relapse-prevention clinical trial,[46] 60 patients with atypical depression (according to Columbia University criteria) of at least 2 years' duration and who had improved with imipramine or phenelzine therapy were stabilized for 6 months and then randomly continued with the same medication or placebo for 6 months. Recurrence rates were 23% for patients receiving phenelzine, 41% for patients receiving imipramine, 47% for patients switched from imipramine to placebo, and 87% for patients switched from phenelzine to placebo. This study demonstrated that chronic atypical depression is highly recurrent if phenelzine is withdrawn 6 months after initial improvement, in contrast with discontinuation from imipramine. Long-term efficacy data are generally lacking in this patient population.

In summary, it appears that MAOIs (particularly phenelzine) may be more effective than TCAs (particularly imipramine) for acute or maintenance treatment of patients with atypical depression, as evidenced by consistent findings in a number of randomized, controlled clinical trials.[29,40-42,46] Studies have reliably shown this effect, but the size of the effect has at times been small, calling into question whether the efficacy advantage of MAOIs in atypical depression patients outweighs the tolerability issues inherent with irreversible MAOIs.

Reversible Inhibitors of Monoamine Oxidase A

As described, most clinical trials of MAOIs in atypical depression have been conducted with phenelzine. Reversible inhibitors of monoamine oxidase A (such as moclobemide) significantly reduce the risks of hypertensive crisis and obviate the need for dietary restriction of tyramine compared with traditional, irreversible MAOIs. However, only a few randomized, controlled trials investigating the efficacy of moclobemide for patients with atypical depression have been conducted to date.[57] In this section, clinical trials of moclobemide versus TCAs[48,49,58] or other agents[59,60] will be discussed. Currently available evidence does not support the superiority of moclobemide over other antidepressants in the treatment of atypical depression, in contrast to data with phenelzine. No studies have directly compared moclobemide with irreversible MAOIs such as phenelzine.

In a relatively small clinical trial, 38 patients with a variety of DSM-III depressive subtypes (episodic, chronic and atypical depressive disorder) were equally randomized to receive moclobemide 100 mg three times a day or clomipramine 50 mg daily for 6 weeks. Both treatments were equally efficacious in this heterogenous sample.[49] In a larger trial (n = 167) by the same team of investigators,[48] moclobemide was slightly inferior to clomipramine and did not show superiority over isocarboxazid for treating the heterogenous depressive sample and, when patients

were subtyped based on the presence of atypical symptoms, there was no interaction between treatment group and depressive subtype.[48] Another study[58] compared moclobemide and clomipramine in a sample of 63 endogenous and non-endogenous depressed patients, employing terminology from early work on atypical depression by West and Dally[18] in 1959. Results from this study are also reminiscent of West and Dally's[18] findings with iproniazid, in that patients with endogenous depression responded better to clomipramine, whereas non-endogenous disorders responded preferentially to moclobemide. Two other small double-blind, controlled clinical trials have compared the efficacy of moclobemide and diazepam in the treatment of atypical depression. Both agents were effective in treating atypical depression, with no significant differences between treatments.[59,60]

5.1.2 Newer Antidepressants

Selective Serotonin Reuptake Inhibitors (SSRIs)

MAOIs (in particular phenelzine) have demonstrated efficacy in the treatment of atypical depression. However, the potentially serious interaction with dietary tyramine, leading to hypertensive crisis, and the risks of drug-drug interactions, leading to serotonin syndrome, have hampered their utility. Safer and more tolerable antidepressants have become first-line treatments for atypical depression.[61] Several randomized, controlled clinical trials support the efficacy of SSRIs for this depressive subtype (fluoxetine vs phenelzine,[43] fluoxetine vs moclobemide,[51] fluoxetine vs imipramine,[52,53] fluoxetine vs nortriptyline[54] and sertraline vs moclobemide[50]).

In open-label trials, fluoxetine has been found to be effective for atypical depression, as defined by the Columbia criteria, showing a response rate of 65%.[62] Recently, our group investigated the effectiveness of escitalopram for treating atypical depression in an 8-week, open-label, flexible-dose, rater-blinded trial.[55] During the study, total 29-item Structured Interview Guide for the Hamilton Depression Rating Scale – Seasonal Affective Disorder (SIGH-SAD) scores were reduced by 53.8% from baseline (33.3) to end of treatment (15.4) [$p < 0.001$]. The atypical symptoms subscale score was reduced by 44.5% from baseline (11) to end of treatment (6.1) [$p = 0.001$]. Sixty-seven percent of patients ($n = 10/15$) were classified as responders at the end of treatment, as defined by ≥50% reduction in SIGH-SAD total score.[55]

Multiple studies have compared response rates (defined by ≥50% reduction in Hamilton Depression Rating score) between SSRIs and MAOIs. In a 6-week, randomized, double-blind study of patients with atypical depression ($n = 40$), the response rates were comparable with fluoxetine 20–60 mg/day (80% response rate) and phenelzine 45–90 mg/day (85% response rate).[43] In contrast, a subgroup analysis of patients with atypical features ($n = 53$) in a 6-week randomized trial of MDD yielded a statistically poorer response rate (defined by ≥50% reduction in Hamilton Depression Rating score) with fluoxetine (55%) compared with moclobemide (67%).[51] A larger, 12-week, randomized study of patients with atypical depression ($n = 197$) found comparable response rates with sertraline (65%) and moclobemide (63%).[50] A recent meta-analysis[56] showed a negligible treatment effect size of 0.02 in favour of MAOIs versus SSRIs (moclobemide vs fluoxetine,[51] phenelzine vs fluoxetine[43] and moclobemide vs sertraline[50]). Data should be interpreted cautiously because two of the included trials used moclobemide, which is presumably less efficacious than phenelzine in the treatment of atypical depression, as discussed in section 5.1.1.[56]

A small randomized, clinical trial of patients with atypical depression ($n = 28$) found no difference between fluoxetine and imipramine, showing both medications to be effective.[53] A subsequent 10-week, randomized, controlled clinical trial in patients with atypical depression ($n = 154$) compared the efficacy of fluoxetine, imipramine and placebo. Comparison of responder rates based on endpoint CGI-I scores showed that fluoxetine and imipramine did not differ from each other in efficacy, and both were significantly more effective than placebo in the intent-to-treat (51% vs 53% vs 23%), minimally adequate trial (58% vs 68% vs 26%) and completer (57% vs 74% vs 30%) groups.[52] Despite a relatively large sample size, the study was insufficiently powered to detect differences between active medications. However, the

study provides robust evidence for the efficacy of fluoxetine based on separation from placebo. Joyce et al.[54] compared response rates (defined as improvement of ≥60.0% in Montgomery-Åsberg Depression Rating Scale[63] scores) between fluoxetine and nortriptyline in a small atypical depression subgroup (n = 16) from a 6-week, randomized, double-blind clinical trial that included 195 patients with MDD. Subgroup analysis demonstrated a superior response rate with fluoxetine (67%) compared with nortriptyline (0%), although conclusions are limited by the small sample size. Overall, the preponderance of data suggests that SSRIs (particularly fluoxetine and sertraline) are superior to placebo and non-inferior to MAOIs or TCAs in the treatment of atypical depression.[29,40-42]

Other Newer Antidepressants

Other relatively new antidepressants, including bupropion, duloxetine, venlafaxine and mirtazapine, have not been systematically investigated in the treatment of atypical depression. Placebo- or comparator-controlled studies are lacking, although several small, preliminary trials have been conducted with bupropion and venlafaxine,[64-66] and an 8-week, pilot clinical trial of duloxetine has been conducted. In this study, 20 patients with atypical depression were treated with duloxetine up to 120 mg/day. Fifty percent responded (defined by a >50% reduction in the 24-item Hamilton Depression Rating score) and 35% remitted (final 24-item Hamilton Depression Rating Scale score ≤7). The small sample size and lack of a placebo control group limits the generalization of the results.[67]

However, because of improved safety and tolerability compared with TCAs and MAOIs, clinicians tend to use these newer antidepressants for MDD patients without regard to the presence of atypicality or other depressive subtype.[20,68] Bupropion may have particular usefulness in the treatment of atypical depression since it has demonstrated substantial utility for depressive symptoms of psychomotor retardation, impaired cognition and fatigue (which are characteristics of atypical depression) in a number of randomized, double-blind clinical trials.[69,70] Bupropion is chemically unrelated to TCAs, SSRIs or other contemporary antidepressants and shares certain pharmacological properties with psychostimulants.

Although the irreversible MAOI selegiline has shown efficacy in treating atypical depression,[38,71,72] the clinical use of this drug has declined because of concerns about dietary tyramine and drug interactions, as well as waning physician experience with this medication. Compared with traditional MAOIs, selegiline is more selective for monoamine oxidase type B, but this selectivity decreases at the higher doses commonly needed for antidepressant activity.[73,74] In this context, a selegiline transdermal system has been developed and approved for treating MDD, with improved adverse effect profiles compared with the conventional oral tablet formulation of selegiline.[73,74] The transdermal delivery system is designed to provide the antidepressant activity of selegiline with markedly reduced risks of interaction with dietary tyramine. Consistent with this premise, a low tyramine diet is not recommended if treatment is restricted to the lowest approved transdermal selegiline dosage of 6 mg/24 h patch. This improvement in safety and tolerability with the selegiline transdermal system may allow clinicians to retain the MAOI class in their arsenal of treatments for atypical depression.[75] Currently available evidence suggests that the selegiline transdermal system (6 mg/24 h, 9 mg/24 h and 12 mg/24 h) is efficacious and well tolerated in both short- and long-term treatment of patients with MDD, particularly those who would obtain the most benefit from treatment with MAOIs.[76-79] However, because of a relative paucity of data, it is premature to conclude that the selegiline transdermal system will offer any incremental value in efficacy over currently available antidepressants in the treatment of atypical depression or whether its adverse effect profile may differ with long-term use.[73]

5.2 Other Agents

Other agents that have shown efficacy for the treatment of atypical depression in randomized, controlled trials or open-label studies include chromium,[80,81] modafinil,[82-84] gepirone,[85]

St John's wort (hypericum),[86] melatonin[87] and growth hormone.[88]

6. Cognitive Therapy

Cognitive therapy has also been proven to be useful as an effective alternative to standard acute-phase antidepressant treatment for patients with atypical depression.[47,89,90]

7. Conclusion

After 5 decades of research, the distinct properties of atypical depression remain somewhat mysterious. In addition, the prevalence of atypical depression may be underestimated as a result of fluctuating diagnostic criteria and methodological differences among studies assessing the prevalence rates. The evolution of diagnostic criteria for atypicality and the extensive research by the group of investigators at Columbia University have led to an emphasis on mood reactivity as the cardinal feature. Continued research is warranted to determine whether other atypical symptoms, such as reverse neurovegetative symptoms, should take diagnostic priority. In addition, opinions continue to differ with regard to the overlap between atypical depression and personality disorders, and the field should continuously strive to integrate past and current research findings to adapt the diagnostic criteria to our best understanding of atypical depression.

There appears to be clinical and scientific utility in differentiating atypical depression from typical depression, in that the former selectively responds to MAOIs compared with TCAs. Further research is needed to fully clarify the role of SSRIs and other newer and more tolerable antidepressants in the treatment of atypical depression. Research to date also indicates that atypical depression is associated with higher rates of psychiatric co-morbidity compared with typical depression, particularly with regard to anxiety disorders, eating disorders and bipolar disorder. Clinicians should be thorough in their evaluations of patients with atypical depression in order to recognize and appropriately treat co-morbid conditions.

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