Current Role of Herbal and Natural Preparations

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Abstract

Depression remains difficult to manage, despite the many registered treatments available. For many depressed individuals, particularly those who have not responded to and/or had adverse effects from standard therapies, herbal and natural medications represent a potentially valuable alternative. This chapter will review several natural remedies used in the treatment of depression. Specific remedies covered include St. John's wort (SJW), S-adenosyl-L-methionine (SAMe), omega-3 fatty acids, rhodiola, and others. We will begin by providing some historical and social context about these remedies. Then we will review efficacy and safety data, as well as biological mechanisms of action of these therapies. Finally, we will discuss the limitations of the current state of knowledge and provide suggestions for a productive research agenda focused on natural remedies. While many questions about these treatments remain unanswered and much work needs to be done before we determine their place in the psychiatric armamentarium, we believe that this chapter will give psychiatrists a good perspective on the pros and cons of herbal and natural antidepressants as part of the pharmacological armamentarium and sensible guidelines on how and when they should be used.

Keywords

5-Hydroxy tryptophan · 5-MTHF · Acetyl-L-carnitine · Alpha lipoic acid · Complementary and alternative medicine · Deplin · Folate · Hypericum · Inositol · N-acetyl cysteine · Natural remedies · Nutraceuticals · Omega-3 · Rhodiola · S-adenosyl methionine · SAMe · St. John's wort

1 General Introduction: Prevalence of Depressive Disorders and Limitations of Current Therapies

Major depressive disorder (MDD) is common and disabling, with a lifetime prevalence of 16.2% (Kessler et al. 2003). From 2000 to 2010, the annual cost of depression in the USA increased by 21.5%, to a total of $210.5 billion (Greenberg et al. 2015), exceeding that of many other diseases. Despite the many antidepressants available, their use is limited by delays in clinical improvement, relatively low rates of response and remission, significant residual symptoms, and high relapse and recurrence rates (Kennedy 2013; Safer 2017). Medication-related side effects may also represent a substantial obstacle to successful pharmacological treatment of depression (Cassano and Fava 2004).

For the significant proportion of patients who are non-responsive and/or intolerant to standard antidepressants, alternative and natural therapies may be compelling. A 2007 National Health Interview Survey reported that in the past year, 38% of adults and 12% of children had used CAM therapies, to an out-of-pocket cost of about $33.9 billion (National Institutes of Health 2010). Many individuals, particularly those with psychiatric disorders, choose to reject US Food and Drug

Administration (FDA)-sanctioned medications in favor of natural products, given the above-mentioned limitations of registered medications or because of personal preferences (Mischoulon 2004; Kessler et al. 2001).

Given the limitations of established therapies, and the growing interest in CAM, there is a need for further research to identify and characterize novel therapies that work via different mechanisms of action, in the hopes of finding an agent that may work faster, better, and with fewer side effects than the current armamentarium of biological therapies. Complementary and natural remedies may represent a potential family of treatments to fill this gap.

2 Natural Products: Introduction

2.1 Common Source of Refined Medications and Challenges with Formulations of Natural Products

Natural and herbal remedies have been used for medical and psychiatric indications for millennia. These products are found in nature and are harvested, processed, and purified to differing degrees depending on the particular standards of each manufacturer and what the local/national regulations may require and allow (Mischoulon 2004). Herbal remedies such as St. John's wort (SJW) may contain hundreds of potentially active chemicals, of which some may be the key psychotropic components (Nierenberg et al. 2008). Other natural remedies, such as SAMe or omega-3 fatty acids, are limited to one or a few chemical components and may therefore be easier to obtain and standardize (Mischoulon 2009). Omega-3 fatty acids, for example, can be readily obtained from fish oil or algae and contain fewer variants.

Consideration of the quality and preparation of different natural remedies is important. For example, SAMe was historically subject to degradation on the shelf, until more stable forms such as tosylated SAMe were developed (Mischoulon et al. 2012a). Without head-to-head comparisons between different preparations, it is difficult to make recommendations about which brand of a particular natural product a patient should or should not use, and the wide variety of options can make product selection complicated and confusing for both doctor and patient.

2.2 Importance of Healing Traditions vs Allopathic Medicine

Natural therapies have historically been widely used throughout Europe and Asia but are relative newcomers to the USA, gaining increased prominence and visibility since the 1990s (Mischoulon and Rosenbaum 1999). Asia in particular has a long tradition of healing and prevention of illness through natural remedies as well as other disciplines such as acupuncture and Traditional Chinese Medicine (TCM) (Kleinman 1975). In South America there is also a tradition of alternative healing, as in the form of curanderos and other types of healers (Risser and Mazur 1995). In

Europe, natural remedies are more strongly integrated into general medical practice, and many licensed physicians use natural products routinely (Fürst and Zündorf 2015).

In the USA, however, there has been more resistance to the adoption of natural remedies, partly due to skepticism on the part of practitioners (Asher et al. 2017), who are trained in the Western model of medicine that historically has emphasized acute treatment rather than prevention of illness and has not included complementary medicine as part of medical school and residency program curricula, though this has been changing with the growing prominence of complementary and alternative medicine. Allopathic medicine also places a great deal of weight on the "gold standard" of randomized controlled clinical trials as the test for whether a treatment is adequate. This "high bar" is especially problematic when dealing with alternative therapies, since many may be harder to blind (e.g., acupuncture and massage) or to deliver in a consistent, generalizable manner (Yeung et al. 2007). For example, therapies such as acupuncture and homeopathy are typically administered in highly individualized regimens for each patient based on the diagnostic tenets of the discipline. In cases where two patients may have the same "Western diagnosis," the TCM diagnosis may differ between both patients, and this could impact the clinician's choice of treatment (Mischoulon et al. 2012b). This makes the development of rigorous double-blind controlled trials difficult and leads to continued reluctance on the part of US physicians to recommend these therapies.

Despite this skepticism, natural remedies are becoming an ever-growing component of health care, and psychiatric conditions are among the most common reasons for which people seek out alternative therapies. Reasons for their popularity include reported effectiveness, easy access without a physician's prescription, and generally superior tolerability compared to standard medications (Mischoulon 2009).

Several caveats need to be considered, however. Natural remedies are not as tightly regulated as drugs registered with the FDA (Mischoulon 2004). The law permits manufacturers to word claims about natural remedies in such a way that does not suggest their product can prevent or cure an illness. For example, antidepressants such as St. John's wort may be marketed as "mood enhancers" or "well-being boosters," claims which do not require FDA oversight or approval. Likewise, unregulated or under-regulated treatments may present certain risks that are not well characterized, since there is no need to obtain approval from the FDA with regard to safety. Economic considerations are also important. Medical insurance plans, whether state-supported or private, generally do not cover herbal and natural remedies, because they have not been approved by the FDA. Consequently, patients who want to use these therapies have to pay out of pocket for them, and many can be quite costly, at times prohibitively expensive with patients of limited means. The costs, risks, and benefits of natural remedies therefore need to be carefully considered by both the practitioner and the patient (Mischoulon 2004).

2.3 The Importance of Research

Given the growing popularity of natural remedies, along with the aforementioned limitations of current registered antidepressant therapies, research on clinical efficacy, safety, mechanisms of action, and cost-effectiveness of natural therapies represents an important scientific endeavor. A better understanding of these remedies could guide physicians about when and when not to recommend them and may help insurance carriers decide whether to cover their costs, as a potential means of reducing more expensive health care utilization, such as inpatient hospitalizations (Ostermann et al. 2017). As it stands, there are relatively few rigorous large-scale RCTs of natural remedies. Most manufacturers of natural remedies do not have the requisite funds to sponsor large studies, which limits their contributions to donating their products for government funded research or at times sponsoring small pilot trials (Mischoulon 2004).

One particularly important reason for continued research is the emergence of serious adverse effects, albeit rare, that have been reported. Notable examples include liver failure associated with the herbal anxiolytic kava (Sarris and Kavanagh 2009), transplant rejection and failure of anti-HIV agents from interactions with SJW (Baede-van Dijk et al. 2000; Markowitz et al. 2003), and sudden death secondary to use of ephedra (Wallace 2003). Continued research on natural remedies is therefore critical from a public health standpoint. An improved understanding of the efficacy and safety of natural products represents an impactful endeavor that could have significant benefits for society.

3 Natural Products Commonly Used for Depression

3.1 St. John's Wort (SJW)

3.1.1 Overview and Efficacy

St. John's wort (SJW; *Hypericum perforatum* L.) is an herbal remedy for depression, studied in over 40 clinical trials (Apaydin et al. 2016), including comparisons against tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) (Apaydin et al. 2016; Linde et al. 2008). The data support SJW as more effective than placebo and being comparable to low-dose TCAs and to standard doses of SSRIs. Tolerability and adherence appear better than for registered antidepressants (Apaydin et al. 2016). However, the published studies are limited by recruitment of patients with milder depression, underreported adverse effects, and often shorter than optimal treatment periods.

3.1.2 Mechanisms

The key psychotropic ingredients of SJW appear to be hypericin, pseudohypericin, and hyperforin (Brockmöller et al. 1997; Seifritz et al. 2016). These chemicals are believed to interact with the hypothalamic-pituitary-adrenal axis to reduce cytokine production, suggesting an anti-inflammatory mechanism of action for SJW.

Likewise, SJW's antidepressant effect may only be partly due to serotonergic activity. SJW also has some mild monoamine oxidase inhibitor (MAOI) activity (Gnerre et al. 2001), but it is thought too modest to contribute to SJW's antidepressant effect.

3.1.3 Dosing

Recommended doses of SJW range from 300 to 1,800 mg/day, usually divided in a twice or three times daily dosing regimen. Different preparations may vary with regard to the amount of active ingredients present, and different brands may therefore differ in efficacy. Commercial preparations are typically standardized based on their hypericin or hyperforin levels (Mischoulon 2009).

3.1.4 Adverse Effects

SJW is generally safe and well tolerated. The most common side effects include dry mouth, dizziness, and constipation (Rodríguez-Landa and Contreras 2003). Increased sensitivity to sunlight (phototoxicity) may occur, which can be prevented by using protection such as sunscreen and hats on occasions where significant exposure to the sun is expected (Clauson et al. 2008). In view of SJW's MAOI activity, there is a concern about serotonin syndrome (hypertension, hyperthermia, flushing, hyperreflexia, dizziness, disorientation, and myoclonus) when combined with other serotonergic drugs (Baede-van Dijk et al. 2000). Combinations with SSRIs are strongly discouraged, though it may be a common practice. Given how frequently SSRIs are prescribed, the risk of this interaction is unknown.

SJW induces the enzyme cytochrome P450 (CYP-450)-3A4, which can reduce clinical effects of warfarin, cyclosporin, oral contraceptives, theophylline, fenprocoumon, digoxin, indinavir, zolpidem, irinotecan, olanzapine, and probably others (Rodríguez-Landa and Contreras 2003). Severe adverse reactions, such as transplant rejection, reduced efficacy of anticancer drugs, and development of resistant HIV strains, have been documented. Cycling to mania may occur in bipolar disorder patients who take SJW when depressed (Nierenberg et al. 2008), so in cases of bipolar depression, SJW should be taken with a mood stabilizer and preferably under clinician supervision. Preliminary evidence suggests that SJW is safe in pregnancy, but in the absence of more conclusive data, pregnant women should probably avoid SJW in favor of antidepressants with more established safety records (Gregoretti et al. 2004).

3.1.5 Conclusion

SJW appears to be a promising natural antidepressant. There are ample small trials and a few larger-scale trials with generally supportive, though mixed evidence. The logical next step would be the continued development of larger-scale trials and more comparisons with standard antidepressants.

3.2 S-Adenosyl-L-Methionine (SAMe)

3.2.1 Overview and Efficacy

S-adenosyl-L-methionine (SAMe) has been used extensively in Europe for decades but arrived in the USA only in the late 1990s (Hardy et al. 2003; Sharma et al. 2017). SAMe is produced by all living beings and functions as a methyl donor in many important physiologic reactions, most notably neurotransmitter synthesis. There are about 50 published clinical trials of SAMe, with administration via oral, intramuscular, and intravenous routes (Galizia et al. 2016; Hardy et al. 2003; Sharma et al. 2017).

SAMe has been successfully combined with TCAs, SSRIs, and SNRIs. Alpert et al. (2004) examined SAMe augmentation in 30 SSRI nonresponders who received open-label therapy with SAMe 800–1,600 mg/day with good results. Papakostas et al. (2010) carried out a double-blind placebo-controlled study of SAMe augmentation in SSRI and SNRI nonresponders. After 6 weeks of treatment with SAMe 800 mg twice daily or placebo, SAMe resulted in significantly greater improvement and response and remission rates than placebo.

A meta-analysis by Hardy et al. (2003) supported SAMe as more effective than placebo and equivalent to tricyclic antidepressants. A more recent meta-analysis of various adjunctive therapies, including SAMe, also supported the use of SAMe in depression (Turner et al. 2014). A recent systematic review (Sharma et al. 2017) also supports SAMe's efficacy but noted that few SAMe studies have emerged in the past 15 years since the Hardy et al.'s meta-analysis. Only one placebo-controlled RCT to date has compared SAMe against an SSRI (escitalopram 20 mg daily) (Mischoulon et al. 2014). This 12-week three-armed study with 189 subjects with MDD used the highest dose of SAMe in a clinical trial (up to 3,200 mg/day). The high placebo response rate resulted in equivalence between the three treatment arms, despite significant improvement for the active treatment arms. Ancillary analyses suggest a gender-related effect favoring men (Sarris et al. 2015), and other investigations suggest that SAMe may help reduce sexual dysfunction in men (Dording et al. 2012).

3.2.2 Mechanisms

SAMe is an intermediate in the one-carbon metabolic cycle, which also involves folic acid and vitamin B12 (Alpert et al. 2008). SAMe formation depends on the enzyme methylene tetrahydrofolate reductase (MTHFR). Genetic polymorphisms can render MTHFR thermolabile, making it less functional and thus unbalancing the one-carbon cycle (Mischoulon et al. 2012c), which may contribute to depression via reduced synthesis of neurotransmitters. SAMe supplements could therefore bypass the MTHFR polymorphism and stimulate neurotransmitter synthesis of serotonin, dopamine, and norepinephrine.

3.2.3 Dosing

The literature on SAMe reports doses ranging from 200 to 3,200 mg/day (Sharma et al. 2017), typically on a twice daily basis. In clinical practice, we have observed

that some patients may require even higher doses to obtain an optimal antidepressant effect.

3.2.4 Adverse Effects

SAMe is well tolerated and safe. Preparations that come in blister packs are preferred, since those have longer shelf lives (Appleton et al. 2016). Gastrointestinal upset appears to be the most common side effect reported (Mischoulon et al. 2014; Papakostas et al. 2010). Other side effects include insomnia, anorexia, dry mouth, sweating, dizziness, and anxiety. Mania and hypomania have been reported in patients with bipolar depression who take SAMe (Mischoulon and Fava 2002; Papakostas 2009). SAMe has few if any interactions with other drugs and is often combined with standard antidepressants and other medications. Pregnancy may result in decreased SAMe and methylation activity. A meta-analysis examining studies of pregnant women with intrahepatic cholestasis found benefit and safety for SAMe (Zhang et al. 2016). Pregnant women with depression may therefore benefit from supplementation, but caution is advised in the absence of more systematic investigations.

3.2.5 Conclusion

SAMe is a promising natural antidepressant. One particular concern that needs to be kept in mind is SAMe is expensive, costing from $0.75 to 1.25 for a 400 mg tablet. Cost-benefit issues therefore need to be considered carefully and discussed between the doctor and patient.

3.3 Omega-3 Fatty Acids

3.3.1 Overview and Efficacy

The omega-3s are long-chain polyunsaturated fatty acids (PUFA) found primarily in fish oil and other marine sources (Appleton et al. 2016). Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are considered to be the primary psychotropic fatty acids in this family (Appleton et al. 2016).

More than 30 clinical trials have tested omega-3 preparations in depressed populations, as adjunctive therapy in subjects with inadequate response to standard antidepressants and also as monotherapy (Appleton et al. 2016; Grosso et al. 2014a; Sublette et al. 2011). Most studies use either EPA or a combination of EPA plus DHA. Doses vary widely, as do the compositions of the preparations. A recent meta-analysis by Sublette et al. (2011) reported that the most effective preparations appear to be those with at least 60% EPA relative to DHA. The various meta-analyses of omega-3s in depressive disorders have shown generally positive but mixed results, which is not surprising, in view of the wide heterogeneity of omega-3 ratios, doses, and study designs (Appleton et al. 2016; Bloch and Hannestad 2012; Grosso et al. 2014b; Lin and Su 2007; Mocking et al. 2016; Sarris et al. 2012; Sublette et al. 2011).

DHA therapy for depression is less well studied (Lewis et al. 2011; Marangell et al. 2003; Mischoulon et al. 2008, 2015). Mischoulon and colleagues found benefit in a double-blind dose-finding study of DHA monotherapy, with a reversed dose-response curve favoring 1 g/day over 2 g/day and 4 g/day. This study was limited by a lack of a placebo arm. Marangell et al. (2003) found no benefit for DHA at 2 g/day, which appears consistent with Mischoulon et al.'s study that found less benefit at 2 g/day or higher (Mischoulon et al. 2008). A more recent double-blind controlled comparison of EPA versus DHA found less benefit for DHA, while EPA appeared more effective in overweight subjects with elevated levels of inflammation (Mischoulon et al. 2015; Rapaport et al. 2016).

Omega-3s have been studied in different forms of depression. Some preliminary evidence suggests benefit in postpartum depression (Freeman et al. 2006; Marangell et al. 2004). In bipolar disorder (Keck et al. 2006; Stoll et al. 1999), the depressive phase of the illness may be more responsive than the manic phase (Sarris et al. 2012). Children and adolescents with depression may also benefit (Trebatická et al. 2017). A large study examining preventive effects of omega-3 and vitamin D for depression in older individuals is underway (Okereke et al. 2018).

3.3.2 Mechanisms

The omega-3s are thought to function in various ways including G-protein signaling inhibition, neuronal membrane stabilization, anti-inflammatory effects, modulation of calcium transport, and possibly others (Stoll 2008; Grosso et al. 2014a). Similarities with lithium's mechanism of action have been proposed (Stoll 2008).

3.3.3 Dosing

Published doses for depression range from as little as <1 g/day to as much as 10 g/day, but most reported doses typically are between 1 and 2 g/day. In unipolar depression, 1–2 g/day of EPA/DHA combination, with $\geq 60\%$ EPA may be a good starting point (Sublette et al. 2011). Studies for bipolar disorder have used between 6 and 10 g/day (Sarris et al. 2012), but caution should be taken with higher doses (see below).

3.3.4 Adverse Effects

Omega-3s are generally well tolerated. Common side effects include stomach upset and fishy taste, which are less frequent now than previously thanks to improved manufacturing standards that reduce impurities. Previous concerns about increased risk of bleeding have been disproven to some degree (Begtrup et al. 2017), though caution is still advised (Gross et al. 2017). Despite their apparent efficacy in the treatment of bipolar illness, cycling has been reported (Stoll 2008), so caution is recommended with this population. Omega-3s are important to the development of the infant brain and pregnancy depletes omega-3 in the mother (Ostadrahimi et al. 2017). Therefore omega-3 supplementation should benefit expectant mothers and their children. Along these lines, fish consumption in pregnancy is supported (U.S. Food and Drug Administration n.d.). However, because we do not have

long-term data on safety or the safest upper limits of omega-3 in pregnancy, caution is advised with pregnant women.

3.3.5 Conclusion

Omega-3 fatty acids are among the more promising natural treatments for depression. Larger-scale studies, dose-finding studies, and mechanistic studies are called for.

3.4 *Rhodiola rosea*

3.4.1 Overview and Efficacy

Rhodiola rosea grows in the mountains of Europe and Asia (Iovieno et al. 2011) and has been used for centuries as an herbal remedy in Asia, Scandinavia, and Eastern Europe. Rhodiola has been studied mostly in Russia and Scandinavia for more than 40 years, though relatively few of these studies have been translated into English. At least four controlled trials support antidepressant effects, anxiolytic effects, and cognitive benefits (Iovieno et al. 2011; Hung et al. 2011), but others have not been so encouraging regarding depression, anxiety, stress, and cognition, though tolerability for rhodiola was good and in one study superior to sertraline's (Cropley et al. 2015).

3.4.2 Mechanisms

Rhodiola's mechanism of action is not well understood. It is proposed to work as an "adaptogen," increasing the body's resistance to external and internal stress and stimulating nervous system activity to improve physical and mental performance. Symptoms that seem particularly good targets for rhodiola include fatigue, stress, depression, and sexual dysfunction (Iovieno et al. 2011).

Rhodiola's "adaptogenic" chemicals include rosavins, salidroside, and p-tyrosol (Ming et al. 2005), as well as antioxidant flavonoids and organic acids. Rhodiola also may modulate monoamines and catecholamines by inhibiting the enzymes MAO-A and MAO-B (Kelly 2001; van Diermen et al. 2009). It may stimulate opioid synthesis and activate central and peripheral opioid receptors (Lishmanov et al. 1997). Finally, rhodiola may reduce secretion of corticotropin-releasing factor (CRF) (Lishmanov et al. 1987; Maslova et al. 1994).

3.4.3 Dosing

Recommended doses range from 100 to 680 mg/day. Rhodiola formulations are usually standardized to a minimum 3% rosavins and 0.8% salidroside (Iovieno et al. 2011).

3.4.4 Adverse Effects

Rhodiola has few side effects, and most are mild and dose-related. These include allergy, irritability, insomnia (including vivid dreams) if taken at night, fatigue, and unpleasant sensations (Iovieno et al. 2011). Rhodiola has few known interactions

and has been combined with TCAs with resultant dampening of TCA side effects (Iovieno et al. 2011). However, mild serotonin syndrome was reported with the combination of rhodiola and paroxetine (Maniscalco et al. 2015). One mouse study supports safety in pregnancy and lactation (Lewicki et al. 2017), but there are no equivalent human studies. While there are no reports of bipolar cycling, rhodiola should probably be used with caution in this population.

3.4.5 Conclusion

Overall, rhodiola appears promising for treating mood disorders. Its clearest indication may be asthenic or lethargic conditions associated with physical or mental strain (Iovieno et al. 2011). Whether rhodiola should be combined with standard antidepressants remains unclear. Combining rhodiola with TCAs, SSRIs, or SNRIs might theoretically diminish their common side effects such as poor memory, sexual dysfunction, and weight gain, but the possibility of serotonin syndrome (Maniscalco et al. 2015) requires caution with such combinations. More controlled studies are warranted.

3.5 Folic Acid

3.5.1 Overview and Efficacy

Folic acid deficiency has been long associated with depression. A few studies of folate supplementation for depression have supported efficacy (Almeida et al. 2015), though the findings are limited by small sample sizes and heterogeneity of folate preparations. L-methylfolate (5-methyltetrahydrofolate; 5-MTHF; Deplin) is approved by the FDA as a medical food to supplement or prevent of vitamin deficiency but has also shown promise as an antidepressant. In a multicenter, randomized, double-blind study (Papakostas et al. 2012), adults 18–65 years of age with MDD and limited response to SSRIs were randomized to augmentation with L-methylfolate 15 mg/day or placebo. The resulting mean change in depression measures from baseline was significantly greater for L-methylfolate than for placebo.

Other L-methylfolate preparations include Cerefolin, which contains 5.6 mg L-methylfolate (Metafolin), 1 mg of vitamin B12 (cyanocobalamin), 50 mg of vitamin B2 (riboflavin), and 5 mg of vitamin B6 (pyridoxine). Its variant, Cerefolin NAC, includes methylcobalamin 2 mg and N-acetylcysteine (NAC) 600 mg (NAC is discussed later in this chapter). Like Deplin, Cerefolin and Cerefolin NAC are approved for the treatment or prevention of vitamin deficiencies and are available by prescription. They are often used off-label for psychiatric indications, including depression, and there is growing evidence of efficacy at slowing down the progression of dementia (Shankle et al. 2016; Hara et al. 2016; Spence et al. 2017). The role of these folate preparations in psychiatric conditions merits further investigation.

3.5.2 Mechanisms

Folic acid is critical in the synthesis of various neurotransmitters and is a key participant in the one-carbon methylation cycle (Alpert et al. 2008). Like SAMe, it is affected by MTHFR polymorphisms that can reduce folate's conversion to 5-MTHF, which is its most active form. Supplementation with Deplin can therefore bypass this polymorphism and also crosses the blood-brain barrier directly to provide needed benefit to the brain.

3.5.3 Dosing

Recommended doses of Deplin are between 7.5 and 15 mg daily (Papakostas et al. 2012). Reported doses of other folate preparations have ranged from 50 to 500 μg/day of folic acid (Mischoulon and Raab 2007) and 15 to 30 mg/day of leucovorin (Alpert et al. 2008).

3.5.4 Adverse Effects

Deplin is very safe and well tolerated with minimal complaints about side effects (Papakostas et al. 2012). Other folate preparations are also considered very safe and well tolerated (Alpert et al. 2008). Concerns have been raised, however, about potential risks associated with folate supplementation, including masking of B12-deficiency anemia, and promotion of cancer (Frankenburg 2009). While the masking of B12 deficiency anemia with folate supplementation is an established risk, newer folate forms such as L-methylfolate (Deplin) are less likely to mask a B12 deficiency anemia and are recommended as the preferred folate form in cases where B12 deficiency may be suspected or under management (Mischoulon et al. 2009). Regarding tumor promotion, evidence for such a role for folate has been mixed (Mischoulon et al. 2009). In the USA, Canada, and Chile, colorectal cancer rates have increased since the introduction of folate fortification (Hirsch et al. 2009), but other investigations have suggested potential benefits and risk reduction (Mischoulon et al. 2009). An extended follow-up of a sample of 6,837 Norwegian ischemic heart disease patients found that supplementation with folic acid plus B12 was associated with increased risk of cancer and cancer deaths, but these results were driven mostly by lung cancer (Ebbing et al. 2009). A recent case-control study suggested an increased risk of prostate cancer associated with higher plasma levels of folate and B12 (Collin et al. 2010). Breast cancer in postmenopausal women has also been linked to high folate intake (Stolzenberg-Solomon et al. 2006). On the other hand, in a recent meta-analysis including almost 50,000 individuals, folic acid supplementation for 5 years resulted in no significant impact on incidence of various cancers (Vollset et al. 2013), and it is worth remembering that folinic acid (leucovorin) is a folate form that has long been used for folate rescue during cancer chemotherapy (Cohen 2017). At this time it is difficult to draw clear conclusions from the literature. We therefore suggest that physicians who are treating patients with a high risk or history of cancer should carefully weigh the risks and benefits of folate supplementation in these individuals.

3.5.5 Conclusion

Folic acid preparations, particularly Deplin, appear as promising augmentative therapies for resistant depression. Large controlled studies are needed in order to provide clearer recommendations about preparation types and dosing.

3.6 5-Hydroxy Tryptophan (5-HTP)

3.6.1 Overview and Efficacy

The amino acid 5-hydroxytryptophan (5-HTP), a serotonin precursor, is obtained commercially as an extract from the African plant *Griffonia simplicifolia* (Iovieno et al. 2011). Most clinical trials of 5-HTP – about 27 in all, including 4 that used active comparators – were conducted in the 1970s and 1980s, based on the serotonin hypothesis of depression (Iovieno et al. 2011). Studies examined combinations of 5-HTP with nialamide, clomipramine, dopamine agonists, or L-tryptophan (L-TRP), and one crossover trial investigated relapse prevention. While 5-HTP outperformed placebo in most trials, often with rapid improvement, the results are limited by small samples, with only six studies showing a statistically significant advantage for 5-HTP. A Cochrane review suggested most of these studies, except for one or two, did not meet criteria for a meta-analysis (Shaw et al. 2002), which does not represent a strong endorsement of the body of work thus far.

3.6.2 Mechanisms

5-HTP is produced chemically from L-tryptophan (L-TRP). The latter can also boost serotonin production, but 5-HTP bypasses conversion of L-TRP into 5-HTP by tryptophan (TRP) hydroxylase, which is the rate-limiting step of serotonin synthesis (Iovieno et al. 2011). TRP hydroxylase may be inhibited by various illnesses and physical or psychological stress, decreasing L-TRP availability. 5-HTP can cross the blood-brain barrier (BBB) for conversion to serotonin (Green et al. 1980; Maes et al. 1990) and may also stimulate synthesis of melatonin, dopamine, norepinephrine, and beta-endorphin.

3.6.3 Dosing

Recommended doses of 5-HTP range from 20 to 3,250 mg/day. 5-HTP is typically started at 50 mg three times daily with meals and titrated upward gradually. Doses are administered on a 2–4×/day schedule, because 5-HTP has a short half-life of about 4 h (Iovieno et al. 2011).

3.6.4 Adverse Effects

The most common adverse effects from 5-HTP are gastrointestinal (nausea, vomiting, and diarrhea) (Iovieno et al. 2011). Gijsman and colleagues recommend combining 5-HTP with a peripheral decarboxylase inhibitor (PDI) that blocks peripheral conversion of 5-HTP to serotonin and decreases GI upset (Gijsman et al. 2002). Less common side effects include headaches, insomnia, and palpitations. Serotonin syndrome has been reported when 5-HTP is combined with

fluoxetine or MAOIs (Lane and Baldwin 1997). However, in one study where single 200 mg doses of 5-HTP were administered to 26 patients taking fluoxetine, none developed serotonin syndrome (Meltzer et al. 1997). Nonetheless, 5-HTP should be used with caution in patients taking antidepressants. There is limited information regarding safety in pregnancy or in patients with bipolar disorder, and caution is therefore advised.

In the 1990s, research on 5-HTP was for the most part discontinued, partly because of the emergence of selective serotonin reuptake inhibitors (SSRIs), and because of outbreaks of eosinophilia-myalgia syndrome (EMS) in 1989 and 1990, which resulted in many fatalities. Despite an FDA ban, it was eventually determined that EMS was the result of bacterial contamination and fermentation and not 5-HTP itself. 5-HTP has since been reinstated on the market, and current data support safety (Iovieno et al. 2011).

3.6.5 Conclusions

After being mostly ignored for almost three decades, 5-HTP deserves reconsideration as a potential antidepressant, and clinical research on this agent should be resumed.

3.7 Inositol

3.7.1 Overview and Efficacy

Inositol is a structural isomer of glucose found primarily in cell membranes as myoinositol. It can be obtained in the diet by eating beans, grains, nuts, and fruits (Moore et al. 1999). There are six small clinical trials of inositol, primarily as augmentation for antidepressants and mood stabilizers in unipolar and bipolar depression (Belmaker and Levine 2008). Inositol outperformed placebo in three controlled studies, and two studies on unipolar depression were negative. Most comparisons in depression, however, did not produce significant differences, likely because of small samples (Iovieno et al. 2011; Mukai et al. 2014).

3.7.2 Mechanisms

Inositol participates in the synthesis of membrane phospholipids and is a precursor in the phosphatidylinositol (PI) cycle, producing inositol triphosphate (IP3) and diacylglycerol (DAG), both second messengers that interact with neurotransmitter receptors (Baraban et al. 1989). Mechanistic similarities to lithium have been proposed to account for inositol's mood-enhancing effects (Belmaker and Levine 2008).

3.7.3 Dosing

Recommended doses range from 6 to 20 g/day, depending on the indication. For depression, doses are typically 12 g/day divided on a two to four times a day basis (Belmaker and Levine 2008; Iovieno et al. 2011).

3.7.4 Adverse Effects

Reported side effects of inositol include mild plasma glucose elevation, gas, nausea, sleepiness, insomnia, dizziness, and headaches (Iovieno et al. 2011). There are no serious toxicities or interactions. Cycling has been reported in bipolar patients, so inositol should be used in combination with a mood stabilizer in bipolar patients (Belmaker and Levine 2008; Iovieno et al. 2011). It not recommended for pregnant women, because it may induce premature uterine contractions (Iovieno et al. 2011).

3.7.5 Conclusion

Inositol appears safe and may alleviate mood disorders, as well as some anxiety disorders, but studies so far are limited by small sample sizes, and larger controlled studies are needed.

3.8 Acetyl-L-Carnitine (ALCAR)

3.8.1 Overview and Efficacy

Acetyl-L-carnitine (ALCAR) belongs to a group of natural products termed "mitochondrial modulators," which are thought to modulate activity of mitochondria and the electron transport chain. Nierenberg and colleagues suggested mitochondrial modulation disruption as a potential factor in bipolar illness (Nierenberg et al. 2013). Placebo-controlled studies of ALCAR in elderly patients with dysthymia or depression have supported efficacy and showed a particularly rapid response (Bersani et al. 2013; Tempesta et al. 1987). A meta-analysis of 12 studies (Veronese et al. 2017) and a systematic review (Wang et al. 2014) have supported ALCAR as more effective than placebo and better tolerated than antidepressants. A study comparing intravenous (IV) and oral ALCAR in alcoholic patients found an advantage for IV ALCAR regarding depressive symptoms such as anhedonia and melancholic and negative symptoms (Martinotti et al. 2011). Not all studies are supportive, however. An RCT in dysthymic patients (Zanardi and Smeraldi 2006) and one in bipolar depression were both negative (Brennan et al. 2013).

3.8.2 Mechanisms

Carnitines are fatty acids that enter the mitochondria as acyl-carnitines and are oxidized to release energy and form acetyl coenzyme A, a factor in the citric acid cycle. ALCAR may protect brain cells by scavenging reactive oxygen species, decreasing oxidative stress, and promoting reactivity to a hostile environment (Nierenberg et al. 2013; Bersani et al. 2013).

3.8.3 Dosing

ALCAR is usually dosed between 1,000 and 3,000 mg/day.

3.8.4 Adverse Effects

ALCAR appears safe and well tolerated. There is one case report of psychosis (Evcimen et al. 2007) and one of mania recurrence associated with ALCAR (Goodison et al. 2017).

3.8.5 Conclusions

Overall, ALCAR appears safe, and there is promising early evidence of efficacy. It is difficult to make recommendations at this time, but further research should be undertaken.

3.9 N-Acetyl Cysteine (NAC)

3.9.1 Overview and Efficacy

N-acetyl cysteine (NAC) is another "mitochondrial modulator," mostly studied in bipolar disorder, but there is some evidence in unipolar depression as well. In a double-blind placebo-controlled trial, 76 subjects with bipolar disorder undergoing treatment as usual (TAU) were randomized for 6 months to augmentation with 2,000 mg/day NAC or placebo, with an advantage for NAC (Berk et al. 2008). A follow-up open trial treated 149 bipolar disorder patients for 8 weeks of NAC 2,000 mg/day and then randomized them to maintenance with NAC or placebo + TAU. There was improvement in the open phase but minimal additional change during double-blind maintenance (Berk et al. 2011). In a 6-month double-blind placebo-controlled trial with 15 bipolar subjects, NAC produced greater improvement in manic symptoms, and depressive symptoms worsened in the placebo group (Magalhães et al. 2013). A study in unipolar MDD found greater remission and response rates in the NAC group after 16 weeks of treatment (Berk et al. 2014).

3.9.2 Mechanisms

N-acetyl cysteine (NAC) increases synthesis of glutathione (GSH), which in turn reduces oxidative stress. It thus prevents oxidative damage in the mitochondrial electron transport chain and protects brain cells. Effects similar to those of lithium and valproate have also been proposed (Data-Franco et al. 2017).

3.9.3 Dosing

Recommended doses of NAC are typically about 2,000 mg/day (Fernandes et al. 2016).

3.9.4 Adverse Effects

Gastrointestinal and musculoskeletal side effects are the most common ones reported with NAC (Kennedy 2013).

3.9.5 Conclusions

Evidence for NAC's benefit in mood disorders is currently very preliminary, and more trials need to be conducted.

3.10 Alpha Lipoic Acid (ALA)

3.10.1 Overview and Efficacy

Studies of alpha lipoic acid (ALA) in animals suggest possible antidepressant effects (Silva et al. 2013, 2016), particularly if BDNF deficiency is involved (de Sousa et al. 2015). A 2-week controlled study of intravenous ALA (600 mg/day) versus mexidol (300 mg/day) in diabetic patients compared effects on affective status, cognitive function, glycemic control, and quality of life. ALA decreased feelings of guilt and increased attention in subjects (Volchegorskiĭ et al. 2011). A combination of ALCAR and ALA in bipolar depression was not encouraging, however (Brennan et al. 2013).

3.10.2 Mechanisms

Alpha lipoic acid (ALA) is a cofactor for the pyruvate dehydrogenase (PDH) complex. It scavenges reactive oxygen species (free radicals) and increases cellular glucose via stimulation of insulin sensitivity. Because insulin activity increases tryptophan influx into the brain (and hence serotonin), insulin sensitivity secondary to ALA supplementation could potentially alleviate depression (Salazar 2000).

3.10.3 Dosing

Typical doses of ALA are about 600 mg/day.

3.10.4 Adverse Effects

Side effects of ALA appear uncommon and include allergic reactions, nausea, and hypoglycemia (Volchegorskiĭ et al. 2011).

3.10.5 Conclusion

ALA appears well tolerated and safe, but evidence thus far is very preliminary, and more systematic human studies in depressed populations are needed to help guide treatment recommendations.

4 The Limitations of Our Current Knowledge and How It Establishes Our Research Agenda

There are scientific as well as safety challenges associated with the use of natural products, either as a monotherapy or as part of combination therapy. At least in the USA, natural products are considered food rather than pharmaceuticals by the FDA, and so they do not undergo the same rigorous preclinical and clinical review as pharmaceuticals (Mischoulon 2004). This limits our knowledge of

pharmacodynamics, pharmacokinetics, animal studies, Phase I–III studies, good manufacturing standards, and post-marketing surveillance of natural products. The paucity of information poses a significant challenge to thoughtful practitioners who want to prescribe natural products as part of a treatment regimen.

One of the greatest fallacies regarding natural products is naïve assumption that "natural" somehow equates with "safe" (Mischoulon and Rosenbaum 1999). Since we frequently do not fully appreciate the mechanisms of action, pharmacodynamics, and pharmacokinetics of even the purported primary active ingredient in a natural product, let alone metabolites or secondary compounds in the product, employing those products either as a monotherapy or in combination with other agents may subject patients to significant unanticipated risks. Even in cases like St. John's wort (SJW; see also Sect. 3.1), where we do have a fair amount of pharmacokinetic data, patients may be subjected to unanticipated drug interactions. In an analysis of the National Ambulatory Medical Care Survey (NAMS) data between 1993 and 2010, SJW was listed 2,300,000 times in the medical record, and 28% of the time a concomitant medication was prescribed that was contraindicated while a patient was taking SJW (Davis et al. 2014).

In a study of 1,466 patients treated in six mental health clinics in Edmonton, Alberta, Canada, 19% of patients were concomitantly taking prescription psychotropic medications and natural products. These patients were 2.8 times more likely to experience a medication-related adverse event when compared with patients who only used prescription psychotropic medications (Necyk et al. 2016). Thus it is incumbent on the practitioner to review the known interactions of a natural product prior to prescribing it and to caution the patient about potential risks.

There is a growing body of evidence about the pharmacokinetic effects of at least the purported key ingredient in some natural products (Hu et al. 2012). A great deal of effort has been spent characterizing the impact of psychotropic medications on the hepatic microsomal systems, since cytochrome P450 enzymes are responsible for over 90% of the oxidative metabolism of most drugs (Na et al. 2011). However, as highlighted by Hu and colleagues in their review of natural products and theranostics, there are other important pharmacokinetic considerations. These include the impact of the compound on the cytochrome P450 (CYP) enzymes in the small intestine as well as the liver (Hu et al. 2012). CYP3A, which is potently induced by SJW, accounts for 70% of the intestinal CYP activity and 30% of hepatic CYP activity (Pal and Mitra 2006). One must also consider the impact of natural products on Phase II conjugation reactions such as glucuronidation or sulfaction, which facilitate biliary and renal excretion. Unfortunately, there are scant data available about the in vivo and in vitro actions of most natural products on these important Phase II reactions (Hu et al. 2012; Mohamed and Frye 2011).

Another important area of pharmacokinetic investigation that requires consideration is the role that transport systems such as the ATP-binding cassette (ABC) and solute carrier (SLC) superfamilies play on the absorption, distribution, and elimination of natural products. Not surprisingly, SJW is the most thoroughly investigated of the natural products with antidepressant properties. SJW is not only a potent inducer of CYP3A4 in the intestine and the liver but is also a potent inducer of the

ABC efflux transporter P-glycoprotein (P-gp). P-gp is extensively expressed and pumps xenobiotics back into the bile duct for excretion and from the proximal tubule of the kidney into urine (Schwarz et al. 2007; Turkanovic et al. 2017). In summary, studies of the pharmacokinetic properties of natural products should investigate their impact not only on protein distribution but also Phase I and Phase II enzymes as well as membrane influx and efflux transporter proteins.

A second area where more extensive investigation is warranted is the study of the pharmacodynamic properties of natural products and their metabolites. Unlike traditional pharmaceutical development, little is known about the binding properties of most natural products. Even less is known about the mechanisms of action of these compounds. This can lead to serious and potentially life-threatening interactions. For example, hyperforin, one of the compounds of St. John's wort, may inhibit the reuptake of serotonin, dopamine, and norepinephrine, and so coadministration with an SSRI or a monamine oxidase inhibitor can potentially have life-threatening consequences (Fasinu et al. 2012). There is even less information available investigating the effects of natural products and their metabolites on second messenger systems of gene expression changes (Hu et al. 2012). There has been one study employing interactive pathway analysis of RNA microarray expression data from neuroglial cell lines to investigate the mechanism of action of *Rhodiola* extract and three of its active constituents (salidroside, tyrosal, and triandrin). Rhodiola and its three active principal constituents altered regulation of 1,062, 1,052, 1,062, and 1,057 genes, respectively, in neuroglial cell lines. The most significant effects of *Rhodiola* were on pathways involved in immune function and modulation, glutamate transmission, G-protein-coupled receptor signaling, c-AMP signaling, and atherosclerosis (Panossian et al. 2014). Again, this work highlights the complexity but also the potential benefit of more detailed study of the impact of natural products at the level of the genome. At this time no one has systematically investigated the effect that natural products might play at modulating the interactions that occur between neurons and glial cells.

An additional area of investigation that might prove fruitful is the interplay between natural products and the human gut microbiome. There are at least three ways one could conceptualize interactions between the gut microbiome and natural products that have antidepressant properties. The natural product could influence the microbiome by changing the makeup of the gut microbiome. This could be accomplished either directly by the bactericidal activity of the product or its metabolites or by introducing exogenous bacteria through probiotics to influence the gut microbiome. Such changes could impact gut permeability as well as the mucus immune and systemic immune systems. A third interaction between the gut microbiome and a natural product involves the metabolism of the natural product into active metabolites that can be absorbed into the portal circulation (Chen et al. 2016).

In summary, there is an exciting opportunity for many further studies of pharmacokinetic, pharmacodynamic, pharmacogenetic, and systems biology approaches to the investigation of natural products with antidepressant effects. These studies are necessary not only to better understand the mechanisms of actions of natural

products and their metabolites but also to ensure the safety of patients employing these therapies.

5 Conclusions

Natural remedies show varying degrees of promise in mood disorders. With continued emergence of quality research studies on efficacy and safety, it is reasonable to expect that some remedies will attain status comparable to standard antidepressants, while others will remain as second-tier agents, and others may be discarded altogether, at least as potential psychotropics. Given the limitations of registered antidepressants, continued research into these agents is warranted so as to determine a place for each in the psychiatric armamentarium.

The best candidates for natural remedies are patients with mild illness who have a strong interest in trying a natural product or are reluctant about registered antidepressants. These individuals are unlikely to suffer from trying a natural agent and can later decide to try a standard agent if the natural remedy proves ineffective. There are also patients who have tried many or most registered antidepressants without benefit, often finding them ineffective or the side effects intolerable. These individuals may also want to try natural remedies, in combination with or as an alternative to standard agents. But these patients are generally more difficult to treat and may not be the optimal candidates for relatively unproven therapies, in view of the risks of untreated or undertreated depression. Clinicians whose patients are considering natural antidepressants should discuss them in depth with their patients and review the pros and cons, particularly efficacy and safety as well as cost-effectiveness.

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