OREGON DUR BOARD NEWSLETTER©

Vol. 2 No. 3 http://pharmacy.orst.edu/ Summer 2000

Practical Considerations for Prescribing Antidepressants In Primary Care

*By: **Michele Koder**, Pharm.D., OSU Coll. of Pharmacy, & **Josh Boverman**, M.D., Asst. Prof., OHSU Dept. of Psychiatry & Family Medicine*

Major depressive disorder (MDD) is a significant public health problem and is frequently encountered by primary care providers. More than 19 million American adults suffer from a depressive illness each year and lifetime prevalence rates may be as high as 12-24%.[1] There is increasing evidence that for many patients, MDD is a lifelong illness resulting in decreased productivity, functioning, quality of life, and increased mortality. Depression is now the leading cause of disability worldwide.[2]

Despite heightened awareness of MDD, many patients do not receive adequate treatment. Approximately 70% of patients do not seek treatment, a fact that may be attributed in part to its social stigma as well as financial and access barriers.[3] In addition, depression is often accompanied by concomitant medical illnesses such as cardiovascular and cerebrovascular diseases, pain syndromes, cancer, substance abuse, and diabetes, which may preclude accurate diagnosis. Finally, treatment options are often associated with suboptimal response rates, intolerable adverse effects, narrow therapeutic indices, and high costs.

Prescribing Trends

The past decade has seen an explosion of antidepressant drug development in an effort to improve safety, tolerability, and treatment outcomes. At present, 22 antidepressants with eight distinct mechanisms of action are available in the U.S.[4] National spending on antidepressants increased by 240% between 1993 and 1998, the largest increase of any therapeutic drug category.[5] In 1999, OMAP's antidepressant costs exceeded $33 million, representing a 50% increase from 1998.

A major reason for this trend is the increased use of costlier new drugs. The average cost per antidepressant prescription has risen by 61.1% in the past decade with the selective serotonin reuptake inhibitors (SSRIs) currently leading the market.[8] Prozac®, Zoloft®, and Paxil® accounted for 71% of total, national antidepressant sales in 1998.[8] In Oregon, SSRIs account for more than $24 million or approximately 70% of total antidepressant expenditures by OMAP.[7] Increased overall antidepressant use for other non-depression indications (OCD, panic disorder, PTSD, social anxiety disorder) and off-label indications (headache and pain syndromes) also contribute. Moreover, public awareness campaigns and direct-to-consumer advertising may be implicated.

Primary healthcare providers are faced with multiple treatment challenges. The aim of this article is to assist providers in optimizing outcomes of patients with uncomplicated MDD. Specifically, it will highlight current treatment guidelines (Part I) and offer assistance in the selection and management of antidepressants (Part II).

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Part I: General Treatment Principles for Uncomplicated MDD

The following recommendations are compiled from practice guidelines endorsed by the Agency for Health Care Policy and Research[11], the American Psychiatric Association[12] and the Technical Advisory Panel on Antidepressant Drugs for the Oregon Health Resources Commission.[10] The reader is encouraged to consult with these guidelines for a more comprehensive discussion of treating depression in the primary care setting.

Essential components of an accurate depression diagnosis include: a thorough medical and psychiatric history, assessment of symptom severity, a survey of life stresses and an evaluation of the family, psychosocial and cultural environment.[12] Treatment goals are 1) to reduce and eliminate target symptoms of the depressive episode, 2) to restore occupational and psychosocial functioning and 3) to reduce relapse and recurrence.[11]

Several effective treatment modalities exist and include drug therapy, psychotherapy, electroconvulsive therapy (ECT), and light therapy. Selection of the treatment plan is highly individual and is dependent on the nature and severity of the depressive episode and patient preference. Primary care providers are encouraged to consult with a mental health specialist to assist in decision making when needed. The remainder of this discussion is limited to antidepressant monotherapy for outpatients with uncomplicated MDD.

Antidepressant treatment is divided into three phases: acute, continuation, and maintenance.

The acute treatment phase aims to eliminate symptoms and to restore functioning.[11] Because 10 to 15% of patients drop out of treatment during this phase, patients should be monitored every one to two weeks for compliance and tolerability of the antidepressant.[11,12] Patients need continuous education on the nature and management of adverse effects and to ensure that they have realistic expectations about time to response. Response, defined as ≥ 50% symptom reduction, should not be assessed before four weeks of continuous therapy.[11] All antidepressants take an average of four to six weeks to produce a response in most patients. If a significant response is achieved by weeks four to six, the antidepressant should be continued for an additional four to six weeks at a therapeutic dose until the patient reaches a full remission.[11] If a partial response is achieved after four to six weeks, the dose of the antidepressant should be increased within the therapeutic range and reassessed by week 12.[11] All available antidepressants produce on average a 60% to 70% response rate.[12] If a patient does not respond after 12 weeks of compliant therapy at an adequate dose, it is recommended to switch to an antidepressant from a different class. A washout period may be required for several days before beginning the new agent.

Treatment outcomes and relapse rates are highly dependent on length of therapy. A high probability of relapse exists in the first eight weeks following acute phase symptom resolution. Full recovery of psychosocial functioning often takes longer. Guidelines recommend continuation treatment with the antidepressant at a therapeutic dose for a minimum of six to nine months following the acute phase.[11,12] Data suggest that continuation treatment may ultimately translate into an overall economic benefit by reducing total health care costs.[29] The importance of continuation therapy is further emphasized

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by the recent addition of length of antidepressant therapy to the HEDIS 2000 quality assurance measures.[30] Intense patient monitoring and follow-up are critical to ensure compliance with continuation therapy.

After six to nine months of successful treatment and complete recovery from an initial episode, providers must determine the need for maintenance antidepressant therapy or drug withdrawal. Approximately 50% to 85% of patients will experience a second episode of major depression in their lifetime.[12] Therefore, the decision to withdraw an antidepressant is highly complex and individual. Providers are encouraged to consult with mental health specialists regarding the benefits and risks for select patients. If drug withdrawal is selected, patient education regarding tapering schedules and early signs of symptom recurrence is critical.[10]

Considerable debate exists regarding the appropriate length of therapy for patients with recurrent depression (>2-3 distinct episodes). Patients having three or more separate and distinct episodes of major depression have a 90% chance of suffering from another episode.[8] In this subset of patients, maintenance therapy is recommended. Treatment durations of one year to lifelong have been advocated.

Part II: Antidepressant Drug Selection

At best, antidepressant therapy has a meager overall response rate considering the average 30% placebo response rates in clinical trials.[10,11] All available drugs are considered equally effective.[10] Drug selection is predicated on history of prior response, potential harmful and/or beneficial effects on concomitant medical and psychiatric disorders and medications, adverse effect profiles, cost, and patient preference. (Table 2) Individual patient characteristics including benefits and risks must be weighed carefully and discussed with the patient. A collaborative treatment plan best assures adherence and success.

Tricyclic Antidepressants

Because of safety and adverse effect concerns, tricyclic antidepressants (TCAs) are rarely first-line therapy in the treatment of depression. However, TCAs are the most widely studied antidepressant agents available. Since their introduction, they have become the reference standard to which new agents are measured. Their efficacy is based on the ability to nonselectively inhibit the reuptake of norepinephrine and serotonin, but their adverse effects are attributed to inhibition of other neurotransmitter systems including histaminic, cholinergic, and alpha-1 adrenergic receptors. Their multiple actions make them useful for a variety of other medical disorders that frequently accompany depression including insomnia, chronic pain syndromes such as headache and fibromyalgia, panic disorder, and allergic rhinitis. Their average 24-hour half-lives afford once-daily dosing. The availability of generic products makes this class the least expensive.

The TCAs are divided into two major subgroups: the tertiary-amine TCAs including amitriptyline and imipramine and the secondary-amine TCAs including nortriptyline and desipramine. At recommended doses, the

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Table 1: SUMMARY OF PHARMACOLOGICAL AND ADVERSE EFFECT PROFILES

Agent	Actions	Anti-cholinergic	Orthostasis	Sedation	Anxiety, Insomnia	Weight Gain	Arrhythmia	GI	Sexual Dysfunction	Seizure Threshold
TCAs										
3° Amines	Histamine blockade Cholinergic blockade α-1 blockade NE reuptake inhibition									
Amitriptyline		+++	+++	+++	-	+++	++	-	•	++
Imipramine		+++	+++	+++	-	+++	++	-	•	++
2° Amines										
Desipramine		++	++	++	-	++	++	-	•	++
Nortriptyline		++	++	++	-	+	++	-	•	++
SSRIs										
Fluoxetine	5-HT reuptake inhibition	-	-	-	+	-	-	+++	†	-
Fluvoxamine		-	-	+	-	-	-	+++	†	-
Paroxetine		-	-	++	-	-	-	+++	†	-
Citalopram		-	-	++	-	-	-	+++	†	-
Sertraline		-	-	-	+	-	-	+++	†	-
Other										
Trazodone	5-HT blockade (low dose)	+	+	+++	-	+	+	+	*	-
Nefazodone	5-HT2A blockade	+	+	++	-	-	?	+	-	-
Bupropion	Dopamine reuptake inhibition	-	-	-	++	-	+	+	-	+++
Venlafaxine	NE reuptake inhibition	-	-	-	++	-	?	+++	†	?
Mirtazapine	Histamine blockade	+	+	+++	-	+++	-	-	†	-
Reboxetine	Selective NE reuptake inhibition	+	+	-	++	?	?	-	†	?

NE = norepinephrine, 5-HT = 5-hydroxytriptamine or serotonin
+++ = high, ++ = intermediate, + = low, - = none, ? = unknown
• = erectile dysfunction with higher doses
† = anorgasmia, erectile dysfunction, decreased libido
* = priapism

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secondary-amine TCAs inhibit only the norepinephrine pump and have lower potency to inhibit histaminic, cholinergic and alpha-1 receptors, and have a more favorable adverse effect profile. Treatment-limiting adverse effects commonly include sedation, dry mouth, urinary retention, constipation, weight gain, and orthostatic hypotension. Due to their poor tolerability, the tertiary-amines are not routinely recommended as first-line agents, particularly in the elderly who are at increased risk of anticholinergic effects and falls. (Table 1) Starting at low doses and titrating slowly upward according to response and adverse effects improves tolerability.[13]

The utility of TCAs are diminished by their potential for a fatal overdose. All TCAs can produce prolongation of QT intervals and lethal cardiac arrhythmias at higher-than-recommended doses (e.g., taking a one to two week supply at once). It is recommended that no greater than one week supply be prescribed at any one time during the acute phase of therapy, particularly with suicide-risk patients. In addition, TCAs can reduce the seizure threshold and should be avoided in patients who have seizure disorders.

Withdrawal phenomena, including diarrhea, urinary frequency, headache, and increased salivation necessitate gradual discontinuation. The risk of withdrawal symptoms increases with duration of treatment and can be avoided by tapering over two to three months, with no greater than a 25% dose reduction per week.

TCAs are involved in several drug interactions. Patients should be carefully monitored when adding or subtracting concomitant medications dependent on metabolism by cytochrome P450 (CYP) -1A2, 2C19, 2D6, and 3A4 enzymes. This class is also prone to drug interactions with drugs that have similar adverse effect profiles. For example, there is an increased risk of orthostatic hypotension when administered with antihypertensive agents.

Although therapeutic dose ranges have been established for some TCAs, the clinical utility is limited and routine drug monitoring is not recommended. Obtaining drug levels may be useful in instances when a patient's health status changes, there is suspicion of noncompliance, or concomitant medications are added or removed which may affect TCA metabolism.

Selective Serotonin Reuptake Inhibitors

The introduction of fluoxetine in 1988 marked the era of the "new generation" antidepressants. Five SSRIs are now available: fluoxetine (Prozac®), paroxetine (Paxil®), sertraline (Zoloft®), fluvoxamine (Luvox®), and citalopram (Celexa®). Promises of reduced toxicity and improved tolerability rapidly led this class to the forefront of the antidepressant market in prescription sales.

SSRIs nonselectively inhibit the reuptake of serotonin (5-HT). As a result, they are largely without the adverse effects that plague the TCAs. In addition to MDD, SSRIs are effective for other psychiatric illnesses including panic disorder, obsessive-compulsive disorder, and social phobia. They may therefore be preferred in patients who possess these conditions in addition to MDD.

The SSRIs have comparable efficacy to TCAs. Their principal advantage is an improved safety profile in overdose and when combined with alcohol. They also are less likely to produce treatment-limiting weight gain. SSRIs, however, do have adverse effects that can be treatment-limiting. (Table 1) 5-HT2 stimulation results in anxiety, insomnia, appetite suppression and sexual dysfunction. 5-HT3 stimulation can produce gastrointestinal distress, nausea, diarrhea, and headache. All SSRIs are likely to produce nausea, vomiting, and diarrhea in approximately 15-35% of patients. Headache is also common and the incidence tends to increase with time. The majority of adverse effects are dose-related. Beginning with a low dose and slowly titrating to the desired dose may help to minimize adverse effects and improve tolerability.

Subtle differences in adverse effect profiles exist among the individual agents and should be considered during drug selection. Fluoxetine and sertraline are associated with appetite suppression and weight loss making them unattractive for patients with anorexia nervosa. Fluoxetine and sertraline are more activating and preferred in patients with hypersomnolent depression, and least preferred in patients with anxiety and insomnia. Paroxetine is unique in that it possesses weak anticholinergic properties, albeit less than the TCAs.

While most adverse effects occur early in treatment, SSRI-induced sexual dysfunction often presents late in therapy posing a difficult situation when patients have responded well. It is therefore important to consider other causes of sexual dysfunction such as undertreated depression itself. It is also important to clarify the chief complaint and nature of sexual dysfunction. Sexual dysfunction with SSRIs is most commonly manifested as anorgasmia and delayed ejaculation although decreased libido can also occur.

A distinguishing feature of fluoxetine is its half-life and duration of action. Most SSRIs have half-lives close to 24 hours, but fluoxetine's is much longer, at approximately 84 hours. Therefore, this agent requires up to a month to reach steady state and to be eliminated once discontinued. Due to this propensity to accumulate, fluoxetine is not routinely recommended in the elderly.

SSRIs differ in their ability to cause drug-drug interactions via the hepatic CYP enzymes. Sertraline and citalopram have the lowest risk of enzyme inhibition making them the SSRIs of choice in patients at risk for drug interactions. The remaining three agents, fluoxetine, paroxetine, and fluvoxamine inhibit one or more CYP enzymes and can cause clinically significant interactions.

Table 2:

GUIDE TO AGENT SELECTION

AGENT	PREFERRED USES	AVOID IN
Tricyclics	• Chronic pain • Migraine • Insomnia • Self-pay • Weight loss • Age < 65 years and likely to tolerate adverse effects	• Suicide or overdose risk • Alcohol abuse • Preexisting arrhythmia or cardiac risk • Preexisting seizure disorder or risk • Age > 65 years and/or increased risk of anticholinergic effects, orthostatic hypotension, and falls • Hypersomnolent depression • Obesity
SSRIs	• Mixed anxiety and depression • Panic disorder • Obsessive compulsive disorder • Social phobia	• History of SSRI-sexual dysfunction
Nefazodone	• Insomnia • Mixed anxiety and depression • SSRI-sexual dysfunction • SSRI failure	• Lack of P450-2D6 isoenzyme • Hypersomnolent depression • Noncompliance
Bupropion	• Smoking cessation • Hypersomnolent depression • SSRI-sexual dysfunction • SSRI failure	• Seizure disorder • Seizure risk factors • Alcohol abuse and eating disorders • Insomnia • Anxiety • Preexisting psychosis
Venlafaxine	• Hypersomnolent depression • SSRI failure	• Uncontrolled hypertension • Insomnia • Mixed anxiety and depression • SSRI-sexual dysfunction
Mirtazapine	• Mixed anxiety and depression • Insomnia • Weight loss	• Hypersomnolent depression • Obesity • SSRI-sexual dysfunction

The SSRIs generally exhibit a flat dose response after reaching a therapeutic plateau. For most patients, increasing the dose beyond those recommended does not provide additional benefit. High-dose trials, under the supervision of a mental health specialist, may be appropriate for treatment refractory symptoms in select patients.

Like the TCAs, all SSRIs except fluoxetine should be withdrawn slowly with no greater than a 25% dose reduction each week. Withdrawal symptoms include dizziness, nausea, vomiting, headache, agitation, insomnia, and flu-like syndrome. They commonly occur within one week after abrupt discontinuation and persist for up to one to two weeks. Paroxetine appears to have the greatest risk for withdrawal syndromes.

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Among the SSRIs, sertraline, paroxetine, and citalopram may be preferred as initial treatment because of the ability to reduce treatment costs by approximately 50% by prescribing half-tablets. These SSRIs are available as scored tablets and the costs of different strengths are about equal. For example, prescribing a sertraline dose of 50 mg a day as sertraline 100 mg, ½ tablet a day results in savings of $369 per patient per year. It is estimated that with effective half-tablet utilization, OMAP expenditures on SSRIs could be reduced by more than $12 million per year.[7]

Trazodone and Nefazodone (Serzone®)

Trazodone and nefazodone are discussed together because of their similar mechanism of antidepressant action. Both agents are weak inhibitors of 5-HT uptake and antagonists of 5-HT2A receptors. However, the clinical utility of these agents differs greatly.

The antidepressant benefits of trazodone are not achieved until doses reach 200 to 400 mg daily. At this dose, most patients will experience significant treatment-limiting sedation because trazodone is a highly potent antihistamine similar to tertiary-amine TCAs.

Nefazodone is a less potent antihistamine than trazodone and is therefore less sedating and better tolerated as an antidepressant. Nefazodone exhibits a dose-related response for depression. While the majority of patients will respond to 300 mg daily, nonresponders may benefit from titration up to 500 mg daily. It is relatively devoid of significant anticholinergic, orthostatic, or SSRI-like sexual dysfunction effects. This agent may therefore be useful in patients with depression and concomitant insomnia and/or SSRI-induced sexual dysfunction. Nefazodone has less seizure, overdose, and cardiotoxicity risk than TCAs.

Sedation, the most common adverse effect of nefazodone, can be minimized with slow dose-titration. Nefazodone is metabolized hepatically to one inactive and two active metabolites by CYP-2D6. Therefore, patients deficient in this enzyme often do not respond to nefazodone therapy. It has been observed in clinical trials to cause visual disturbances such as blurred vision and trails in up to 9% of patients. Nefazodone has a short half-life and requires twice daily dosing.

Bupropion (Wellbutrin®)

Bupropion inhibits both dopamine and norepinephrine reuptake. Its pharmacologic profile is similar to psychostimulants such as methylphenidate, so bupropion is considered an "activating" antidepressant. Consequently, it is not recommended in patients with agitation, anxiety or insomnia.

This agent is particularly useful in patients with atypical or hypersomnolent depression and in nonresponders to TCAs and/or SSRIs. Bupropion is also FDA-approved for smoking cessation and may be favored in depressed smokers. Its lack of sexual side-effects makes it a good choice for patients with a history of SSRI-induced sexual dysfunction.

Bupropion's adverse effect profile is minimal in comparison to TCAs and SSRIs. (Table 1) However, bupropion is the most potent antidepressant in lowering the seizure threshold. This risk is both dose-dependent and formulation-dependent. The seizure risk is largely based on use of the original immediate-release product and is reduced with the use of the newer, sustained-release product at doses of <450mg/day. Bupropion can also exacerbate psychotic symptoms in patients who have an underlying predisposition to psychoses. As with nefazodone, twice-daily dosing is required and is suboptimal in patients with a history of noncompliance.

Venlafaxine (Effexor®)

Venlafaxine is a novel antidepressant that dose-dependently inhibits 5-HT, norepinephrine, and dopamine reuptake. At low doses (e.g., 75 mg daily) venlafaxine primarily functions as an inhibitor of 5-HT reuptake and is similar to the SSRIs. At medium to high doses (e.g., 375 mg daily) it becomes a potent inhibitor of norepinephrine reuptake similar to desipramine. When pushed to even higher doses, dopamine reuptake inhibition occurs. Therefore, patients who do not respond to lower doses may benefit by dose escalation. Venlafaxine lacks effects on alpha-adrenergic, cholinergic, and histaminic receptors.

Venlafaxine has a unique adverse effect profile and an ability to induce sustained, dose-related elevations in blood pressure. It should be used with caution in patients with hypertension. Similar to the SSRIs, venlafaxine lacks the safety concerns of the TCAs, but causes a high incidence of gastrointestinal disturbances (nausea and loose stools) and sexual dysfunction. This drug is often activating and at high doses produces anxiety and insomnia. It appears to be weight-neutral with both weight gain and weight loss reported. Venlafaxine is also associated with a withdrawal syndrome and a slow taper is recommended upon discontinuation.

Venlafaxine undergoes extensive first-pass metabolism by CYP-2D6 to an active metabolite that is then excreted renally. Prolonged elimination may occur in patients with renal and hepatic disease.

Mirtazapine (Remeron®)

Mirtazapine is a direct blocker of histamine receptors, specific serotonin (5-HT2A, 5-HT2C, and 5-HT3) receptors, and alpha-2 adrenergic receptors. Antidepressant efficacy is postulated to be the result of increased availability of serotonin at the 5-HT1A receptor.[4]

Mirtazapine's adverse effect profile is also distinct. (Table 1) First, because it blocks serotonergic transmission at 5-HT2 and 5-HT3 receptors, mirtazapine lacks the anxiogenic effects and the sleep, sexual, and gastrointestinal disturbances frequently seen with SSRIs. Therefore it is an alternative for patients with a history of SSRI-intolerance. Consistent with 5-HT2C blockade, mirtazapine causes increased appetite and weight. Mirtazapine-induced weight gain was significant enough to cause approximately 8% of patients in clinical studies to discontinue the medication. Mirtazapine may be beneficial in patients with weight loss. It is a highly potent histamine blocker at low doses and causes sedation in similar magnitude to amitriptyline. Sedation was the most common reason for drop-outs in clinical studies but may provide clinical utility in patients with insomnia.

Mirtazapine undergoes extensive hepatic metabolism. Its effects on the CYP system and concomitant medications are as yet undetermined. Mirtazapine is similar to amitriptyline without the cardiotoxicity or overdose risk. Dosing is simple. It can be initiated at the target dose, 15 mg, and taken once daily.

Reboxetine (Vestra®)

Reboxetine is the newest antidepressant developed. This agent received an "approvable" status upon preliminary review by the FDA in July 1999.[19] Expected to be available in 2000, it is a novel non-tricyclic selective norepinephrine reuptake inhibitor (SNRI). Reboxetine is currently available in the United Kingdom and Europe under the names Edronax® and Norebox®. It has little to no affinity for adrenergic, cholinergic, or histaminic receptors and dopaminergic or serotonergic reuptake. It is therefore devoid of the classical adverse effects of the TCAs and SSRIs.

At present there is limited published data available. The original new drug application (NDA) submitted in April '98 is based on data from two short-term and one long-term placebo-controlled, non-U.S. studies involving approximately 900 hospitalized patients and outpatients with MDD.[20] Upon request by the FDA, the manufacturer has submitted additional data from two studies conducted in the U.S. that were mid-trial during the original submission. One study showed positive results, whereas the other study did not reveal significant differences between either reboxetine, fluoxetine or placebo for the primary endpoint.[21]

The most commonly reported adverse effects in clinical trials were dry mouth, constipation, and insomnia.[21-27] Final FDA approval is pending evaulation of the additional data.

Monoamine Oxidase Inhibitors (MAOIs)

Two MAOIs with proven antidepressant efficacy are available in the US: tranylcipromine (Parnate®) and phenelzine (Nardil®). MAOIs inhibit

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monoamine oxidase, an enzyme that metabolizes serotonin, dopamine, and norepinephrine in the CNS. This is thought to account for the antidepressant efficacy of these medications.

Unfortunately, these medications are associated with severe, life-threatening interactions with common foods and a number of medications – including most antidepressants. Prescription of MAOIs is recommended only by specialists and only after other options have been exhausted. In patients taking MAOIs, all new prescription or over the counter drug recommendations should be discussed with the patient's psychiatrist and/or a pharmacist.

Conclusion

In summary, care for patients suffering from uncomplicated MDD continues to pose a significant challenge despite the availability of new antidepressant treatment options. The "newer" or second- and third-generation agents do not provide superior efficacy over their predecessors. They generally have improved safety in overdose and with alcohol compared to older TCAs, but may cause other treatment-limiting side effects. Furthermore, the unit cost per prescription of the new agents are in some cases 10 times that of the old agents. (Table 3)

Table 3: Dosing and Cost

Agent	Usual Target Dose	Typical Regimen	Cost* per year ($)
Amitriptyline (generic)	150 mg	150 mg qHS	66
Imipramine (generic)	150 mg	3 x 50 mg qHS	230
Desipramine (generic)	150 mg	2 x 75 mg qHS	66
Nortriptyline (generic)	50-100 mg	2 x 50 mg qHS	124
Fluoxetine (Prozac®)	20 mg	20 mg qAM	884
Paroxetine (Paxil®)	20 mg	½ x 40 mg qD	430
		1 x 20 mg qD	790
Citalopram (Celexa®)	20-40 mg	½ x 40 mg qD	354
		1 x 20 mg qD	682
		1 x 40 mg qD	711
Sertraline (Zoloft®)	50-100 mg	½ x 100 mg qD	391
		1 x 50 mg qD	760
		1 x 100 mg qD	783
Nefazodone (Serzone®)	300-400 mg	150 mg BID	802
Bupropion SR (Wellbutrin SR®)	150-450 mg	150 mg BID	992
Venlafaxine (Effexor®)	75-375 mg	75 mg BID	890
Mirtazapine (Remeron®)	15-30 mg	½ x 30 mg qHS	408
		15 mg qHS	793

*Cost based on average wholesale price (AWP) - 11% or HCFA maximum allowable cost (MAC), Drug Topics Redbook July 2000 Update

To complicate matters, there is scarce, credible data available comparing the adverse effects and cost-effectiveness of antidepressants. Among the newer agents, SSRIs have been the most widely studied against placebo and older agents such as TCAs in randomized, controlled clinical trials of short-duration (6-8 weeks). A recent analysis of 315 trials provides a summary of the safety and efficacy of new versus old antidepressants.[28] No significant differences were observed in efficacy rates among new agents and first- and second-generation TCAs (data from 150 trials), or each other (data from 32 trials). Compiled data indicate the overall response rates were approximately 50%. When analyzing overall drop out rates (average of 30%), the investigators found no statistical difference between new and old agents. Drop out due to adverse effects were slightly higher for first-generation TCAs than for SSRIs (16% vs. 11%, CI=2-6) and did not differ among SSRIs or other new agents and second-generation TCAs or tetracyclic agents.

Providers should note that in general, antidepressant trial results are often difficult to interpret and compare due to the inherent heterogeneity of patients, small sample sizes, inadequate description of study settings, infrequent analysis of secondary outcomes such as quality-of-life and functional status, and variability in data collection of adverse event rates.[28] In addition, there is little data available regarding the efficacy and safety of antidepressants to guide clinical decision making in special populations (e.g., the elderly, pregnant/nursing women, or pediatric/adolescent patients) and in patients with significant co-morbid conditions. The treatment of such patient subsets as well as the treatment of refractory or drug-resistant depression is best guided under the supervision of a mental health specialist.

Drug selection must therefore be considered on an individual basis taking into account patient profiles, concomitant conditions, patient preferences, the potential for short- and long-term adverse effects, and cost. ◙

Article Reviewers: William H. Wilson, MD, Associate Professor of Psychiatry, OHSU; Dr. Constance Powell, Oregon Psychiatric Association, and Ann Hamer, Pharm.D., OSU College of Pharmacy.

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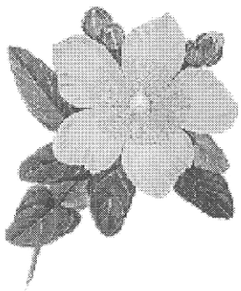
St John's Wort Interactions



*by **Helen Varley**, B. Pharm., Dip. Clin. Pharm., MRPharmS and **Michele Koder**, Pharm.D.*

Many patients are turning toward "natural" products and dietary supplements for a variety of medical conditions in the hopes of avoiding the problems associated with pharmaceuticals. St John's Wort, also coined "natural Prozac," is increasing in popularity in the U.S. This product, derived from the plant *Hypericum perforatum,* has been used for centuries in other cultures for the treatment of a variety of depressive and other disorders.[1] The majority of clinical experience with this extract is centered in Germany where it is licensed for treatment of anxiety, sleep disorders and depression.[2]

The pharmacologic, safety, and efficacy profile of St John's Wort remains largely unknown. The hypericum extract may contain up to 10 or more constituents that exert pharmacologic effects.[2] Debate exists as to which extract(s) are primarily implicated in mediating antidepressant activity. Current research suggests that two major constituents, hypericin and hyperforin, potentially inhibit serotonin, norepinephrine, and dopamine reuptake and/or inhibit monoamine oxidase activity.[2]

Information regarding the efficacy of St John's Wort in the treatment of depression is increasing. A meta-analysis of 23 controlled studies including 1,757 mild-to-moderately depressed outpatients compared St John's Wort with placebo (n=15) and other antidepressants (n=8).[2] St John's Wort was standardized to the hypericin content (0.4 to 2.7 mg daily) while the dose of the whole herb varied widely (300 to 1000 mg daily). Efficacy was evaluated by standard depression scales such as the Hamilton Depression Scale and the Clinical Global Impression Scale. St John's Wort was significantly superior to placebo, equally effective and better tolerated than the antidepressant agents amitriptyline, imipramine, and maprotiline.[2] Caution should be used when interpreting these results as all the studies included in the analysis were small, of short duration (four to eight weeks), evaluated widely variable doses and preparations, and used lower-than-standard doses of the tricyclic antidepressants.[2] The safety and efficacy of St John's Wort in the treatment of depression therefore remains inconclusive and undefined. Results of US studies evaluating the efficacy of St John's Wort, that are being funded by the National Institutes of Health, are awaited.[1]

The popularity of St John's Wort continues to increase, however, and this may be partly due to the common misconception that natural products/supplements are safe and free of adverse effects. In recent months, there have been several case reports of significant drug interactions involving St John's Wort in the medical literature.[3-10] The use of St John's Wort with prescription drugs without forethought and careful monitoring can lead to significant drug interactions.

Reported cases have most frequently involved interactions with cyclosporine, warfarin, oral contraceptives, and theophylline; drugs which are metabolized by hepatic cytochrome P450 (CYP). It is believed that St John's Wort increases metabolism of these agents through induction of hepatic CYP isoenzymes in the liver (CYP 3A4, 1A2, and 2C9).[4,5,6,10]

Two cases of acute heart transplant rejections were associated with the use of St John's Wort while taking cyclosporine.[6] In both cases, cyclosporine plasma concentrations were reduced after initiation of St John's Wort and symptoms of acute transplant rejection developed. When the St John's Wort was discontinued cyclosporine levels returned to the therapeutic range.[6]

A pharmacokinetics study in eight healthy volunteers has shown a significant interaction exists when the protease inhibitor indinavir and St John's Wort are taken together. Indinavir plasma concentrations eight hours after dosing, were reduced by a mean of 81% when indinavir and St John's Wort were taken concurrently.[4] It is possible that similar interactions may occur with any of the protease inhibitors (PIs) or non-nucleoside reverse transcriptase inhibitors (NNRTIs), which are metabolized by the same pathway.[5] Such interactions could have very severe consequences as low plasma concentrations of protease inhibitors are a cause of antiretroviral resistance and treatment failure.[4]

St John's Wort may also induce the intestinal P-glycoprotein transporter which functions as a toxin defense mechanism by pumping absorbed toxins and/or drugs back out into the lumen. This system is responsible for decreasing the oral bioavailability of a number of drugs including cyclosporine and digoxin.[6,7,8] A study of 25 healthy volunteers has shown that multiple dose treatment with St John's Wort causes significant reductions in the digoxin levels. Peak and trough digoxin levels were reduced by 25% and 33% respectively after 10 days of concurrent therapy with St John's Wort.[7]

Additional reports suggest St Johns Wort may interact with psychoactive medications including SSRIs through a different mechanism.[3] Concurrent use of St John's Wort, which may increase serotonin, norepinephrine and dopamine levels, produced symptoms of central serotonin excess when taken with sertraline or nefazodone.[9] Symptoms of serotonin excess include changes in mental status, tremor, gastrointestinal upset, headache, myalgia and restlessness.[9] Similar interactions may occur if St John's Wort is used with "triptan" migraine therapies.[10]

In February 2000 the FDA issued a health advisory letter to health professionals, warning of potential drug interactions associated with St John's Wort.[5] They recommended against the concomitant use of St John's Wort and protease inhibitors or non-nucleoside reverse transcriptase inhibitors and warned that other prescription drugs such as oral contraceptives and drugs used in the treatment of heart disease, depression, seizures, certain cancers and transplant rejection may be affected by St John's Wort.[5] Table 1 includes drugs which may potentially interact with St John's Wort.[10] The recommended course of action for any patients taking any drug listed is to discontinue the St John's Wort. Suggestions for monitoring these patients during the transition period are shown.

It is becoming increasingly important for providers to discuss the use of non-prescription therapies, such as St John's Wort, with their patients so

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that significant clinical drug interactions can be avoided. A recent survey found 18.4% of adults taking regular prescription medication also took at least one herbal product or high dose vitamin. Of those using alternative therapies, 61.5% did so without informing their provider.[11]

Article Reviewer: James Slater, Pharm.D., Clinical Pharmacy Specialist, Providence Medical Group.

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Table 1 – Summary of St John's Wort Drug Interactions

Drug	Effect of St John's Wort	Suggested management after discontinuation of St John's Wort
HIV Protease Inhibitors indinavir, nelfinavir, ritonavir, saquinavir, amprenavir	Reduced blood levels with possible loss of HIV suppression	Measure HIV RNA viral load
HIV non-nucleoside reverse transcriptase inhibitors delavirdine, efavirenz, nevirapine	Reduced blood levels with possible loss of HIV suppression	Measure HIV RNA viral load
Anticoagulants warfarin phenprocoumon	Reduced or increased anticoagulant effects reported	Monitor INR closely as this may rise on stopping St John's Wort. Dose of anticoagulant may need adjusting.
Immunosuppressants cyclosporine rapamycin tacrolimus	Reduced blood levels with risk of transplant rejection	Drug levels may increase after stopping St John's Wort, dose may need adjusting.
Oral contraceptives ethinyl estradiol	Reduced effect with risk of pregnancy and breakthrough bleeding	
Anticonvulsants carbamazepine, phenobarbitone, phenytoin	Reduced blood levels with increased risk of seizures	Anticonvulsant levels may increase on stopping St John's Wort, dose may need adjusting.
Cardiovascular digoxin, diltiazem, nifedipine digitoxin, beta blockers	Reduced blood levels with loss of control of heart rhythm or heart failure	Digoxin and digitoxin levels may increase on stopping St John's Wort, dose may need adjusting. For other treatments and monitor therapy accordingly.
Respiratory theophylline	Reduced blood levels and loss of control of asthma or chronic airflow limitation	Theophylline levels may increase on stopping St John's Wort, dose may need adjusting.
CNS imipramine, amoxapine, amitriptyline	Reduced blood levels	
SSRIs: citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline	Increased serotonergic effects with increased incidence of adverse effects	
Triptans: sumatriptan, naratriptan, rizatriptan, zolmitriptan	Increased serotonergic effects with increased incidence of adverse effects	
Chemotherapy cyclophosphamide, tamoxifen, taxol, etoposide	Reduced effect	

Adapted with permission of the UK Medicines Control Agency [10]

We hope you found this issue of the Oregon Drug Use Review Board Newsletter useful as well as thought-provoking and interesting. We welcome your questions, concerns, comments or ideas regarding the newsletter. Address correspondence to the managing editor:

Kathy L. Ketchum, Coordinator of Medicaid Programs
OSU College of Pharmacy, 840 SW Gaines, Mail Code: GH212, Portland, OR 97201-3098
E-mail: ketchumk@ohsu.edu; Phone: (503) 494-1589; Fax: (503) 494-8797

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