Utah Medicaid Pharmacy & Therapeutics Committee

Drug Class Review

Antidepressants, Monoamine Oxidase Inhibitors (MAOIs)
28:16:04.12

Isocarboxazid (Marplan®, generic)

Phenelzine (Nardil®, generic)

Selegiline (EmSam®)

Tranylcypromine (Parnate®, generic)

Anti-Parkinson Agents, Monoamine Oxidase B Inhibitors (MAO-B)
28:36.32

Rasagiline (Azilect®)

Selegiline (Eldepryl®, Zelapar® and generic-*for some products*)

Final Report
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Executive Summary

Introduction: This review includes the nonselective monoamine oxidase inhibitors isocarboxazid, phenelzine and tranylcypromine, labeled for use in the treatment of depression as well as the specific monoamine oxidase-B inhibitors (MAO-B) selegiline and rasagiline. Indicated for the treatment of depression, the non-specific monoamine oxidase inhibitors are available in tablet formulation as are the MAO-B medications. Selegiline is additionally available in transdermal formulation (EmSam®) for use in depression. Both MAO-B inhibitors (rasagiline and selegiline) are indicated for the treatment of Parkinson's disease. Rasagiline is available as an oral tablet and selegiline is available as oral tablet, capsule and orally disintegrating tablet formulations. The transdermal formulation of selegiline is not labeled for use in Parkinson's disease.

Monoamine oxidase inhibitors (MAOIs) have been available for use for over 60 years following the discovery that the antitubercular drug iproniazid had mood-elevating properties. MAOIs are categorized in a variety of ways. By chemical structure they are either hydrazine (phenelzine, isocarboxazid) or non-hydrazine (rasagiline, selegiline and tranylcypromine) compounds. By MAO enzyme selectivity, they demonstrate MAO-A, MAO-B or mixed selectivity. Categorized by enzyme binding affinity they demonstrate either reversible or functionally irreversible binding to monoamine enzymes. MAOIs are highly active antidepressants, however their use has been limited by a number of coincident occurrences. First, the FDA required efficacy studies on medications marketed before the 1960s, including the MAOIs. At this same time, morbidity and mortality reports were being published that found the MAOIs "unsafe", although the connection with tyramine intake, which could be controlled, was not known. Finally, a study of the Medical Research Council in 1965 compared a (too) low dose of phenelzine (60 mg daily) over a too short duration (4 weeks) with a new tricyclic (imipramine) in inpatients with severe endogenous depression and found imipramine to have superior efficacy. Imipramine also appeared better tolerated, albeit the TCA side effect profile had not been fully defined. These events are most responsible for the current disuse of the MAOIs. By the 1970s, investigators identified MAO subtypes, MAO-A and MAO-B. MAO-B degrades dopamine and was found in high concentration in the basal ganglia of the brain. MAO-B inhibition resulted in increased dopamine concentrations in the brain and these agents began to find their utility in the treatment of Parkinson's disease, a disease of brain dopamine deficiency.

Clinical Efficacy: Evidence is insufficient to identify differences in efficacy between MAOIs. A review of the evidence finds that comparative evidence between MAOIs or MAO-Bs is scarce. In the treatment of depression, MAOI efficacy appears to persist for at least 6 months. Available evidence suggests that phenelzine may be superior to isocarboxazid in inpatient treatment of depression while no difference was found between phenelzine and tranylcypromine in treatment-resistant depression. Evidence suggests that compared to TCAs, MAOIs may be especially useful in the treatment of atypical depression. Although efficacious in the treatment of bulimia nervosa and social anxiety disorders comparative evidence is unavailable. Evidence does not support the use of MAOIs in smoking cessation. There are no comparative trials with selegiline transdermal therapy for depression. Rasagiline was found efficacious in the treatment of Parkinson's disease fatigue although comparative evidence is unavailable. Evidence found no increase in mortality with use of MAO-B agents in the treatment of Parkinson's disease.

Comparative evidence is lacking for MAO-B therapies in Parkinson's disease. MAO-B therapy was not more effective than other anti-Parkinson therapies, but may be better tolerated.

*Adverse Drug Reactions***:** MAOIs may increase the risk of suicidality in young people and may activate mania/hypomania in patients with undiagnosed bipolar disorder. Rapid discontinuation of MAOI therapy may precipitate a withdrawal reaction. Early adverse events include postural hypotension which may be minimized with slow dose uptitration, administration of fluids, divided or bedtime dosing. Late adverse effects include weight gain, paresthesias (which may be minimized with pyridoxine supplementation), hypoglycemia, tremor and blood dyscrasias. MAOIs (especially maprotiline) lower the seizure threshold and should be used cautiously in patients with a history or risk of seizures. Although rare, hepatotoxicity may occur (especially with phenelzine and isocarboxazid) and patients should be instructed to note and report signs and symptoms of hepatotoxicity. Transdermal selegiline may cause application site reactions, problems with impulse control, hallucinations and falling asleep while performing activities of daily living. Rasagiline appears well tolerated, although adverse event rates are higher in the elderly.

Hypertension may occur in the absence of interacting medications or diet. More commonly, hypertensive crisis may occur when MAOIs are ingested with high-content tyramine foods (>6-10 mg/serving). Transdermal selegiline at 6 mg/24 hours is void of this interaction although risk increases with higher doses. MAOIs are highly toxic in overdosage, affecting cardiac conduction and requiring hospitalization and careful monitoring while the drug is eliminated from the body.

MOAIs bind monoamine oxidase irreversible and exert effects until monoamine is regenerated, which may require up to 14 days. MAOIs impair oxidative degradation of vasoactive amines and stimulant type medications. Hepatic enzyme inhibition (CPY2C19) increases serum levels of substrates (e.g. omeprazole, citalopram, sertraline) and the effect persists after the MAOI is discontinued. Caution is required in adding medications in patients who receive an MAOI or have had one recently discontinued. Of particular concern is the risk for serotonin syndrome. Use of an MAOI and additional medication which increases serotonin levels, especially one that increases serotonin by a different mechanism, may result in serotonin syndrome which may be fatal. Medications carrying the greatest risk in combination with an MAOI are the SSRIs and linezolid. The syndrome may occur in a dose-dependent fashion with the weak serotonin inhibitors meperidine, tramadol, methadone, fentanyl and dextromethorphan. Serotonergic interaction with the tricyclic antidepressants is greatest with clomipramine.

Summary: The MAOIs are not first–line therapy for the treatment of depression as safer alternatives are available, although they may afford a benefit for patients with resistant or atypical depression. Comparative evidence is lacking for the nonselective MAOIs as well as the MAO-B inhibitors. Due to irreversible MAO-binding, caution must be exercised when using these medications. Safety issues include fatal serotonin syndrome and hypertensive crisis, as well as cardiotoxicity, lowering of the seizure threshold and interactions with other CYP2C19 metabolized medications and substrates.

Introduction:

MAOI medications have been available for use for over 60 years following the discovery that the antitubercular drug iproniazid had mood-elevating properties.[1,2] Five MAOIs are currently available for use in the US. These agents are categorized in a variety of ways. By chemical structure they are either hydrazine (phenelzine and isocarboxazid) or non-hydrazine (selegiline and tranylcypromine) compounds. By MAO enzyme selectivity, they demonstrate MAO-A, MAO-B or mixed selectivity. Categorized by enzyme binding affinity they demonstrate either reversible or functionally irreversible binding.[1] MAOIs are highly active antidepressants, however their use has been limited by a number of coincident occurrences.[3,4] First, the FDA required efficacy studies on medications marketed before the 1960s, including the MAOIs. At this same time, morbidity and mortality reports were being published that found the MAOIs "unsafe", although the connection with tyramine intake, which could be controlled, was not known.[5] Finally, a study of the Medical Research Council in 1965 compared a (too) low dose of phenelzine (60 mg daily) over a too short duration (4 weeks) with a new tricyclic (imipramine) in inpatients with severe endogenous depression and found imipramine to have superior efficacy. Imipramine also appeared better tolerated albeit the TCA side effect profile had not been fully defined.[3,4] These events are most responsible for the disuse of the MAOIs. By the 1970s, MAO-B which degrades dopamine, was found in high concentration in the basal ganglia of the brain.[5] MAO-B inhibition increased dopamine concentrations in the brain and these agents found their utility in the treatment of Parkinson's disease, a disease of brain dopamine deficiency.

Included in this review are the nonselective MAOIs isocarboxazid, phenelzine and tranylcypromine labeled for the treatment of depression as well as the MAO-B specific agents selegiline and rasagiline. Both MAO-B inhibitors are indicated for the treatment of Parkinson's disease; transdermal selegiline is additionally indicated for use in depression. Each of the agents is available in oral dosage forms as tablets. Selegiline is additionally available as oral capsule, orally disintegrating tablet and extended-release transdermal patch formulations. See **Table 1** for a comparison of the agents.

Table 1: Comparison of Monoamine Oxidase Inhibitor Antidepressants[6-8]

	Available Formulations	Indications/Uses	Oral Dose Range, Adults	Oral Dose Range, Pediatrics	Generic
Isocarboxazid (Marplan®)	Marplan Oral Tablet: 10 mg	Depression	Depression Initial: 10 mg twice a day. May increase every 2 to 4 days by 10 mg and after one- week increase by up to 20 mg weekly. MAX: 60 mg/day in 2-4 divided doses. Then increased up to 20 mg weekly. Doses above 40 mg daily are not well studied. Maintenance: After several weeks, slowly taper to the lowest effective dosage.	Not established in children under 16 years old	No
Phenelzine (Nardil®)	Oral Tablet: 15 mg Nardil, Oral Tablet: 15 mg	Depression: Atypical, non-endogenous, or neurotic Unlabeled Use Agoraphobia, bulimia nervosa, social phobia	Depression Initial: 15 mg three times a day. Increase as tolerated to 60-90 mg daily. Maintenance: After maximal therapeutic effect is obtained, titrate over several weeks to the minimum effective dose. Bulimia nervosa: 60-90 mg daily	Not established	Yes
Rasagiline (Azilect®)	Azilect: Oral Tablet 0.5 mg, 1 mg	Parkinson's Disease	Parkinson's disease Monotherapy or Adjunctive Therapy Not receiving levodopa: Initial: 1 mg daily MAX: 1 mg daily Receiving levodopa +/- other Parkinson medications: Initial: 0.5 mg daily, may increase to 1 mg daily based upon response. MAX: 1 mg daily Caution: Wait 5 weeks after fluoxetine D/C to begin Rasagiline. Wait 14 days after D/C Rasagiline to begin meperidine, tramadol, methadone, propoxyphene, monoamine oxidase inhibitors (MAOI; including	Not established	No

			other selective MAO-B inhibitors), tricyclic antidepressants, SSRIs, or SNRI therapy.		
Selegiline (EmSam®, Eldepryl®, Zelapar®)	Oral Capsule: 5 mg Oral Tablet: 5 mg Eldepryl: Oral Capsule: 5 mg Zelapar: Oral Tablet, Disintegrating: 1.25 mg Emsam: Transdermal Patch, Extended Release: 6 mg/24 HR, 9 mg/24 HR, 12 mg/24 HR	Major Depressive Disorder (Emsam®) Parkinson's disease as adjunct therapy to levodopa/carbidopa (Eldepryl®, Zelapar®) Unlabeled Use Dementia HIV, Alzheimer's disease – Dementia, Amyotrophic lateral sclerosis, Attention deficit hyperactivity disorder, Depression, Narcolepsy, Parkinson's disease, (initial treatment), Periodic limb movement disorder, Schizophrenia (adjunct), Tardive dyskinesia	Orphan drug designation for idiopathic, postencephalitic or symptomatic Parkinsonism (paralysis agitans) used adjunctively with levodopa/carbidopa. MAX: 10 mg daily oral tablet, 2.5 mg daily orally disintegrating tablets Parkinson's disease adjunctive with levodopa/carbidopa Oral tablet/capsule: 5mg twice a day (oral tab/cap) with breakfast and lunch MAX: 10 mg/day Orally disintegrating tablet: Initial: 1.25 mg once daily for 6-weeks minimum. May increase after 6 weeks to max dose 2.5 mg daily. (No eating or drinking 5 min. before or after dosing). Do no start selegiline before 5 weeks after discontinuing fluoxetine or 4-5 half-lives (1 week) for carbamazepine, SSRIs, SNRIs, clomipramine, imipramine, meperidine, tramadol, methadone, pentazocine, propoxyphene, or dextromethorphan. Transdermal: Major depressive disorder Initial: 6 mg/24 hr (20 mg/20 cm) patch daily. Increase dose by 3mg/24 hours every 2 weeks. MAX: 12 mg/24 hours	Orphan drug designation for idiopathic, postencephalitic or symptomatic Parkinsonism (paralysis agitans) used adjunctively with levodopa/carbidopa. Oral: Not established in pediatric patients. Transdermal: Contraindicated in children < 12 years Efficacy not established in children 12-17 years	Yes (oral) No (transdermal)
Tranylcypromine (Parnate®)	Oral Tablet: 10 mg Parnate Oral Tablet: 10 mg	Major depressive disorder, without melancholia Unlabeled Use: Depression, Combination therapy,	Major depressive disorder, without melancholia Initial: 10 mg three times daily. May increase after 2 weeks by 10 mg daily every 1-3 weeks. MAX: 60 mg daily	Not established	Yes

		Depression/Panic disorder, Dysmorphophobia, Obsessive-compulsive disorder, Pure autonomic failure, Seasonal affective disorder, Social phobia, Subcortical leukoencephalopathy			

Disease Overview

<u>Major Depressive Disorder</u>

The mood disorders (including major depressive disorder, bipolar I disorder, bipolar II disorder, cyclothymic, persistent depressive disorder (dysthymia) and premenstrual dysphoric disorder) affect approximately one in ten adult Americans.[9] Major depressive disorder is the most common of the mood disorders, affecting nearly 15% of US adults.[10] In 2004, depression was listed as the third most common cause of disease burden across the world.[11] In general, depression occurs more frequently in women than men, in people 40-50 years of age and in patients living below the poverty level. Depressive disorder is linked to increased rates of chronic disease, health care utilization and impaired activities of daily living. Almost half of all patients with depression experience inabilities to maintain healthy work, home and social habits. The economic burden of depression in the US (~$83.1 billion in 2000) results from increased rates of indirect costs (unemployment, lost productivity, etc.) in addition to direct healthcare costs.[12-14] Depression is frequently underdiagnosed and, even more frequently, depression is inadequately treated. Improving disease education and increasing access to care will help to improve clinical outcomes and save costs.[15]

A Behavioral Health Barometer for Utah by the Substance Abuse and Mental Health Services Administration (SAMHSA) reveals that compared to the US as a whole, youth age 12-17 as well as adults in Utah were more likely to have a major depressive episode.[16] For youth, the rate of a major depressive disorder in Utah compared to the US during 2011/2012 was 10.2% vs 8.7% and in 2012/2013 it was 11.5% vs 9.9%. For adults over the same time periods the rates were 5.1% vs 4% and 5.4% vs 4.1%, respectively.[16]

Depression is a serious mental disorder characterized by changes in cognitive and physical behaviors with a loss of pleasure in enjoyable activities.[15] Major depression is defined as the presence of at least 5 symptoms during a period of at least 2-weeks that reflect a change in previous functioning and causes distress or impairment in normal activities. Symptoms associated with a depressive episode must include sadness and/or loss of interest or pleasure. Other symptoms may include significant unexplained weight loss, insomnia or hypersomnia, agitation, fatigue, feelings of worthless, excessive guilt, reduced ability to concentrate and recurrent thoughts of death. In <2% of the general population depression is not clearly associated with acute distress, impairment or change from previous functioning. The diagnosis of dysthymic disorder includes a persistent depressive mood with chronic ($\geq$2 years), ongoing symptoms that tend to be less severe and/or numerous.[15] Depression with atypical symptoms is a depressive subtype associated with mood reactivity. The diagnosis is made when at least two of the following symptoms are present, significant weight gain or increase in appetite, hypersomnia, leaden paralysis, or a long-standing pattern of interpersonal rejection sensitivity without meeting criteria for melancholic or catatonic features.[17]

Drug therapy is the foundation of the medical management of the mood disorders. Before the introduction of the second-generation antidepressants, drug therapy was limited to tricyclic antidepressants and monoamine oxidase inhibitors, known collectively as the first-generation antidepressants. The first generation antidepressants are associated with many intolerable adverse effects (sedation and anticholinergic effects) and are no longer agents of choice for treating most depressive disorders. As a result, the second-generation antidepressants, including

the selective serotonergic agents and serotonin modulators, have become one of the most commonly prescribed drug classes in the US pharmaceutical market, accounting for $10.9 billion in US prescription sales in 2003.[18] Clinical evidence suggests the most efficacious treatment for depression includes a combination of psychological therapy and medication therapy for at least 6-8 weeks.[19] The goal in treating depression is to reduce the risk of disease/symptom recurrence.[12] There is little evidence to demonstrate one agent or class of antidepressants is more effective than others. A response rate of 70% may be achieved with 6-8 weeks of most any pharmacotherapy. Titration schedules should be conservative, with modest increases from the initial dose each 3 weeks to allow for a clinical response. Aggressively increasing doses may reduce tolerability and increase adverse events. Patience is the key to successful outcomes because it may take 12 weeks for substantial benefit.[20] Treatment is generally continued for 6 to 12 months after stabilization.[20] Almost half of all patients being treated for depression by their primary care provider will discontinue their medication therapy within a month, unless proper education and a treatment plan is provided.[21] Selection of an antidepressant agent should be based on treatment history, comorbid conditions anticipated side effects, clinical evidence and patient preference.[15,22] In patients demonstrating suicidal ideation, the drug selected should have low toxicity if taken in overdose.[12,15,22]

Clinical guidelines for the treatment of depression include the World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders Part 1(2013)[23] and Part 2 (2015)[24], the National Institute for Health and Clinical Excellence (NICE) Depression in adults: recognition and management (2009)[25], National Collaborating Center for Health, Mental: The Treatment and Management of Depression in Adults (2010)[26], the American Psychiatric Association Practice Guideline for the Treatment of Patients with Major Depressive Disorder (2010)[27], Institute for Clinical Systems Improvement (ICSI): Adult Depression in Primary Care (2016)[28], Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical Guidelines for the Management of Major Depressive Disorder in Adults (2016)[29], and the American Academy of Child and Adolescent Psychiatry (AACAP): Practice Parameter for the Assessment and Treatment of Children and Adolescents with Depressive Disorders (2007).[30] See **Table 3** for a summary of the most current guideline recommendations.

The choice of an initial antidepressant should consider the severity of symptoms, comorbid conditions, psychosocial stressors, biological, psychological, environmental factors, safety, tolerability, anticipated side effects, pharmacologic medication properties (cytochrome P450 (CYP) hepatic enzyme interactions, half-life, drug interactions), cost, patient preference, prior treatment experiences and family history of response. Patients should be advised that a response to therapy may be delayed 4-6 weeks.[15,31] First-line agents include a second-generation antidepressant (e.g. SSRI, SNRI, mirtazapine, bupropion) for the treatment of depression. If only a partial response is achieved at 4-6 weeks, the dose may be increased (if tolerated) for another 4 weeks. Partial responders may receive an alternative antidepressant, a combination of antidepressant agents or adjunctive treatment with another class of medications including lithium, thyroid hormone, atypical antipsychotic agent or dopamine agonists. A large randomized controlled trial examining Sequenced Treatment Alternatives to Relieve Depression (STAR*D) reported no differences in efficacy between the adjunctive medication classes.[32] Medication therapy should be adjusted until a full remission is achieved. Non-responders should be referred to a mental health specialist. MAOIs are restricted to refractory treatment. Treatment should

continue for an additional 6-9 months to prevent relapse. Chronic maintenance therapy is recommended in patients with two or more depression episodes. Cognitive Behavioral Therapy (CBT) is recommended for all patients with depressive disorders.[15]

Table 2. Current Clinical Practice Guidelines for the Treatment of Depressive Disorders

Guideline	Recommendations
World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for biological treatment of unipolar depressive disorder Part 1: (2009)[23]	Medication therapy in combination with psychological counseling is recommended A treatment plan and disease/medication education are recommended for all patients First-line: Antidepressants No single class of antidepressants has proven to be more effective than another Amitriptyline, clomipramine and venlafaxine have demonstrated increased efficacy in severely depressed hospitalized patients Newer agents (bupropion, trazodone, SSRI, SNRIs, mirtazapine) are generally better tolerated than the older agents In treatment-resistant patients: Consider increasing the dose, switching to another antidepressant agent, combining two antidepressants, augmenting the antidepressant with another agent (best evidence for aripiprazole, lithium, quetiapine)
World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for biological treatment of unipolar depressive disorders. Part 2: Maintenance Treatment of Major Depressive Disorder (Updated 2015)[24]	<u>Adults</u>: Continue the antidepressant which induced remission or lithium if augmentation was successful. If this fails, consider the combination of antidepressant/lithium. Continue the medication at the same treatment dose Effective agents include • Tricyclic antidepressants (TACAs), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs) and selective serotonin norepinephrine reuptake inhibitors (SNRIs). o Newer antidepressants have better long-term efficacy due to better tolerability and better safety profile compared with older agents (TCAs) • Some data supports quetiapine in maintenance therapy • Evidence is lacking for carbamazepine or other mood stabilizers. Duration of maintenance therapy • Discontinuation should always be gradual over at least 3 months. • Acute depressive episode: 6-9 months • Recurrent depressive episode in the prior 5 years or difficult to achieve remission: 3 years • Those at greatest risk: Having a new episode of depression within 1 year after 2 or 3 attempts to discontinue therapy. <u>Children and Adolescents</u>

Guideline	Recommendations
	SSRIs and SNRIs have limited evidence the continued medication is better than placebo in preventing new episodes with differences in suicidality between groups Older Adults Evidence supports use compared with placebo for nortriptyline (tachycardia and dry mouth more common), phenelzine, paroxetine, escitalopram, citalopram but NOT sertraline.
National Institute for Health and Clinical Excellence (NICE) Depression in adults: recognition and management (2009)[25]	Mild-Moderate Disorder First-line: low-intensity psychosocial intervention Second-line: antidepressant therapy (typically SSRI) OR a high-intensity psychosocial intervention Moderate-Severe Disorder First-line: combination antidepressant therapy and a high-intensity psychological intervention Antidepressant agents - SSRIs have a favorable risk-benefit ratio - Fluoxetine, fluvoxamine and paroxetine are associated with increased risk of drug interactions - Venlafaxine and tricyclic antidepressants are associated with increased risk of death from overdose - Monoamine oxidase inhibitors (MAOIs) should only be prescribed by specialists - In treatment-resistant patients, increase dose or switch to another antidepressant
National Collaborating Centre for Mental Health (UK): Depression British Psychological Society; National Institute for Health and Clinical Excellence (2010)[26]	Step 1: All known and suspected presentations of depression - Assessment, support, psychoeducation, active monitoring and referral for further assessment and interventions Step 2: Persistent subthreshold depressive symptoms; mild to moderate depression - Low-intensity psychosocial interventions, psychological interventions, medication and referral for further assessment and interventions - Depression with anxiety: Treat depression first - Anxiety disorder with comorbid depression: Treat anxiety first - Sleep hygiene, active monitoring, low-intensity psychosocial interventions, group cognitive behavioral therapy - Do not use antidepressants routinely with subthreshold depressive or mild depression because the risk-benefit is poor. - Drug therapy is appropriate: Past history of moderate severe depression or subthreshold depression for at least 2 years or symptoms which persist after other interventions - Do not use St John's wort.

Guideline	Recommendations

	Step 3: Persistent subthreshold depressive symptoms or mild to moderate depression with inadequate response to initial interventions; moderate and severe depression
	• High-intensity psychological interventions, combined treatments, collaborative care and referral for further assessment and interventions (Counseling and psychodynamic psychotherapy alone is of uncertain effectiveness)
	• Medications: SSRI +/- psychological intervention
	• SSRIs are preferred due to a favorable risk-benefit ratio
	   ◦ SSRIs increase the risk of bleeding (geriatric, drug-interaction)
	   ◦ Fluoxetine, fluvoxamine, paroxetine higher drug-drug interaction potential
	   ◦ Paroxetine has more discontinuation symptoms than other SSRIs
	• Consider toxicity in overdose (TCAs carry the highest risk)
	• MAOIs should only be prescribed by a specialist
	• Doxepin should NOT be prescribed
	• Consider adherence relative to side effects
	   ◦ Venlafaxine exacerbates cardiac arrhythmias
	   ◦ Hypertension exacerbated with venlafaxine/duloxetine
	   ◦ TCA induced postural hypotension and cardiac arrhythmias
	• Lack of response at 3-4 weeks: Increase the medication dose or switch
	• No evidence suggests treating depression different by subtype, gender, sex or ethnicity
	• Switching antidepressants: No evidence suggests a difference with between or within classes. Try newer antidepressant SSRI/SNRI again then consider a different less-well tolerated class.
	   ◦ Consider: fluoxetine long half-life; fluoxetine/paroxetine increase TCA levels, from one serotonergic agent to another due to serotonin syndrome, waiting 2 weeks for non-reversible MAOI washout before starting new agent.
	• Augmentation: Lithium, antipsychotic, mirtazapine. Do NOT augment with benzodiazepine, buspirone, carbamazepine, lamotrigine or valproate, thyroid hormones or pindolol.
	Step 4: Severe and complex depression; risk to life; severe self-neglect
	• Medication, high-intensity psychological interventions, electroconvulsive therapy, crisis service, combine treatments, multi-professional and inpatient care
	• Depression with psychotic symptoms: Augment with antipsychotic (dose and duration unknown)

Guideline	Recommendations

American Psychiatric Association: Practice Guideline for the Treatment of Patients With Major Depressive Disorder (2010)[27]	Acute phase
	 First-line: antidepressant medication (SSRI, SNRI, bupropion, mirtazapine)
	 • The effectiveness of antidepressant medications is comparable and initial selection is based on adverse effect profile, prior treatments, cost and patient preference
	  o If side effects occur, lower dose or switch agents
	  o If no response or partial response: increase dose, switch agents or augmenting the antidepressant with another antidepressant or a non-antidepressant medication (lithium, thyroid hormone or a second generation antipsychotic)
	
	 Continuation phase
	 • Continue successful treatment for 6-9 months and monitor for signs of relapse
	
	 Maintenance phase
	 • Continue successful treatment in patients with three or more depressive episodes or with additional risk factors for relapse
	
	 Discontinuation of treatment
	 • Taper the medication over the course of at least several weeks
	
	 Other notes
	 • Combination of antipsychotic and antidepressant medications is recommended in patients with psychotic symptoms

Institute for Clinical Systems Improvement (ICSI): Major Depression in Adults in Primary Care (2016) [28]	Recommended pharmacotherapy: • SSRIs, venlafaxine, duloxetine, desvenlafaxine, mirtazapine, bupropion Other options: • Secondary amine tricyclics (TCAs), monoamine oxidase inhibitors (MAOIs) Augmentation therapy: • Bupropion, buspirone, mirtazapine, triiodothyronine (T3), stimulants, TCA-SSRI combination, lithium, atypical antipsychotics Recommended in patients with treatment-resistant or partially-responsive disease: Referral to a mental health specialist
Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical guidelines for the	Selection • Based on disease severity, comorbid conditions, adverse effect profile, treatment history, potential drug–drug interactions, patient preference and cost; Use of antidepressant should be

Guideline	Recommendations
management of major depressive disorder in adults (2016)[29]	accompanied by patient education, close monitoring (1-4 weeks) and self-management techniques First-line recommendations • Bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, milnacipran, mirtazapine, paroxetine, sertraline, venlafaxine Second-line recommendations • Amitriptyline, clomipramine and other tricyclic antidepressant (TCA) agents; quetiapine; selegiline; trazodone Third-line recommendations • Phenelzine, tranylcypromine

American Academy of Child and Adolescent Psychiatry (AACAP): Practice Parameter for the Assessment and Treatment of Children and Adolescents with Depressive Disorders (2007) [30]	A confidential relationship should be maintained with the child or adolescent
	
	Psychiatric assessments should routinely be made
	
	Treatment should always include an acute and continuation phase, some may require maintenance treatment
	
	First-line: Supportive psychotherapy
	
	Second-line: Psychotherapy and/or antidepressants
	   o Selective serotonin reuptake inhibitors (SSRIs) are the most commonly used pharmacotherapy in pediatric patients
	   o Clinical response should be assessed at 4-week intervals
	      ▪ If inadequate response, increase dose
	   o Treatment should be continued for 6-12 months
	   o Atypical antipsychotics, combined with SSRIs, are recommended as the treatment of choice for depressed psychotic pediatric patients

Parkinson's Disease

Parkinson's disease (PD) has been noted historically since 5000 BC.[33,34] It became recognized as a medical condition in 1817 when James Parkinson published "An Essay on the Shaking Palsy" based on 6 cases in his practice.[35] By the mid twentieth century dopamine was synthesized and research indicated that a deficiency of dopamine, localized in the brain striatum, was likely responsible for the symptoms of Parkinson's disease.[33,34]

Parkinson's disease is second only to Alzheimer's disease as the most common neurodegenerative disease.[34] PD affects 10 million persons worldwide and approximately 1 million in the US.[36] PD is predominantly a disease of the elderly. The prevalence is 1% in those over 65 years, although 4% of cases are identified in younger persons.[36,37] Life expectancy is unchanged but quality of life is affected.[36] Most patients are unable to continue full time work

within 4-5 years of diagnosis.[36] The costs of PD are significant; direct and indirect costs associated with treatment, social security payments and lost income is estimated at $25 billion in the US yearly.[37] Average per patient medication costs are $2500 yearly with therapeutic surgery estimated at $100,000 per patient.[37] Risk factors include advanced age, male sex, low estrogen levels, agricultural work (presumed pesticide exposure), low folate levels and head trauma (especially as a child). The genetic marker alpha-synuclein is associated with a 1.5-fold increased risk and evidence demonstrates a low correlation with disease and a positive family history.[33,34,38]

Parkinson's disease symptoms arise from progressive degeneration of dopaminergic neurons in the substantia nigra of the midbrain, resulting in a deficiency of striatal dopamine.[34,36] Many symptoms of Parkinson's disease are the result of striatal dopaminergic deficiency resulting from a progressive loss of neurons.

The diagnosis of PD is a made clinically.[36] Diagnosis requires the presence of the cardinal feature, bradykinesia and one other cardinal manifestation; resting tremor, rigidity, bradykinesia or gait impairment/postural instability. Symptoms present asymmetrically.[39] Other common features include disturbances in speech, mood, cognitive function, autonomic disturbances, sexual dysfunction, hyposomia (loss of smell), gastroparesis/constipation, insomnia, dream enactment and dementia.[34]

As the disease progresses and parkinsonian symptoms impact the person's life, treatment with dopaminergic therapy is initiated either with levodopa/carbidopa or a dopamine agonist.[34,36,40] Levodopa is the most effective agent for motor symptoms but long-term levodopa use is associated with movement disorders. The choice of initial medication is made in consultation with the patient. Considerations include drug efficacy, safety, ease of administration, costs, patient age, comorbidity, work status, expectations and assessment of the trade-off required to provide better symptom control while preventing/delaying dyskinesias. Rudolph recommends first-line use of dopamine agonists in young people who tolerate the slow dosage uptitration and side effects well, in order to stave off the development of movement disorders.[36] In older patients, levodopa/carbidopa is considered first-line. Older patients with impaired gait and balance disturbances benefit from optimizing motor function which may prevent a fall.

Over time, the effects of levodopa become less predictable and persist for shorter periods of time. Additionally, levodopa side effects become more significant, including dyskinesia, akathisia, "on-off" phenomena and freezing.[33,34,41] [34,36,40] Wearing-off is common with levodopa therapy. As the duration of levodopa activity declines over time, levodopa-carbidopa must be dosed more frequently or with a higher dose. As the disease progresses, additional medications may be added to the treatment regimen. Amantadine works to reduce movement symptoms and levodopa-induced dyskinesias. Catechol-O-methyl transferase (COMT) inhibitors prolong the effects of levodopa. Anticholinergics can reduce tremor, but must be used cautiously in the elderly. When maximal pharmacotherapy fails, surgical options including deep brain stimulation may be considered.

It was expected that MAO-B inhibition would be useful in the treatment of Parkinson's disease via inhibition of dopamine metabolism resulting in increased CNS dopamine concentrations.[5,34,42] Treatment with nonspecific MAOIs was associated with significant side effects (hypertension, dyskinesia and toxic delirium) voiding their clinical utility. Selegiline and

rasagiline are MAO-B specific agents. They are used as adjunctive therapy, in low doses, and produce only mild side effects.[5,42] As soon as the diagnosis of Parkinson's disease is made, many clinicians would start a patient on a monoamine oxidase type B (MAO-B) inhibitor. MAO-B inhibitors provide mild symptomatic benefits (depression, fatigue, motor symptoms), reduced off-time and are neuroprotective. Finally, as the disease progresses resulting in inadequate control or wearing-off, the use of combination therapy including dopamine agonists and levodopa-carbidopa is initiated.[34,36,40]

Clinical guidelines for the treatment of Parkinson's disease include the Canadian Guideline on Parkinson's Disease (2012)[43], the European Academy of Neurology Guideline on Early (uncomplicated) Parkinson's Disease (2011)[44], the European Academy of Neurology Guideline on Late (complicated) Parkinson's disease (2011)[45], and practice parameters from the American Academy of Neurology on Neuroprotective Strategies and Alternative Therapies for Parkinson Disease and Treatment of Parkinson Disease with Motor Fluctuations and Dyskinesia (2006).[46] **See Table 4** for a summary of the most current guideline recommendations. In general, the guidelines recommend first-line therapy for treatment of motor symptoms with levodopa-carbidopa or a dopamine agonist, with some bias for use of levodopa in younger patients. MAO-B inhibitors are sometimes considered a first-line option. As the disease progresses, combination therapy with levodopa and dopamine agonists is recommended. Guidelines give further recommendations for managing on-off phenomena, wearing-off phenomena, freezing, and dystonias. Movement fluctuations are managed by adjustment of the levodopa dose, frequency of administration, addition of a COMT agent (non-ergot class is preferred) or MAO-B medication. Off-time may be reduced with dopamine agonists. Dyskinesias may respond to amantadine therapy. Anticholinergics and beta-blockers are useful in the management of tremor. Most documents include recommendations for the treatment of non-motor problems; autonomic dysregulation, sleep, mood and cognitive changes. Surgical interventions are recommended when medication therapy has failed.

Table 3. Current Clinical Practice Guidelines for the Treatment of Parkinson's Disease

Guideline	Recommendation

Canadian Guideline on Parkinson's Disease (PD) (2012)[43]	• Do not withdraw or discontinue abruptly to prevent akinesia or neuroleptic malignant syndrome
	• Do not practice "drug holidays" due to the risk of neuroleptic malignant syndrome
	• Exercise great caution in assuring continuation of the prescribed regimen when admitted to hospital or care facility
	• Be aware of dopamine dysregulation syndrome
	
	Motor Symptoms in Early PD
	• First-Line Pharmacological therapy
	  o Levodopa at the lowest possible dose. Avoid modified-release formulations
	  o Dopamine agonists (DA), may try more than one agent
	    ▪ Non-ergot dopamine agonists are preferred. Ergot DA require testing renal function, erythrocyte sedimentation rate, chest radiograph
	  o MAO-B inhibitors (selegiline, rasagiline)
	
	Second-Line Pharmacological therapy

	• Amantadine
	• Anticholinergics for symptomatic treatment
	• Beta-adrenergic antagonists for postural tremor
	
	Motor Symptoms in Later PD
	• First-Line pharmacological therapy
	   o Motor fluctuations: Entacapone and Rasagiline reduce off time
	   o Reduce off-time: Pramipexole and ropinirole
	• Second-line pharmacological therapy
	   o Motor fluctuations: Modified-release levodopa formulations
	   o Motor fluctuations with dyskinesias: Amantadine
	
	Depression
	• Individually tailor to the individual.
	• Consider amitriptyline
	
	Psychotic symptoms
	• Reduce polypharmacy. Reduce/stop anticholinergics, anxiolytics, sedatives
	• Reduce/withdraw precipitating antiparkinsonian medication
	• Reduce/stop anticholinergics, amantadine, dopamine agonists, MAO-B and COMT inhibitors, lastly reduce levodopa. Motor symptoms may worsen
	• Mild symptoms may not require treatment
	• Clozapine (with registration), quetiapine. Do NOT use olanzapine, phenothiazines or butyrophenones
	
	Dementia
	• Discontinue aggravators: anticholinergics, amantadine, TCAs, benzodiazepines, tolterodine and oxybutynin
	• Treat with donepezil or rivastigmine
	
	Additional Pharmacotherapy may be indicated for sleep, autonomic dysfunction (urinary dysfunction, weight loss, dysphagia, constipation, erectile dysfunction, orthostatic hypotension, hyperhidrosis, sialorrhea)

Neuroprotective strategies and alternative therapies for Parkinson disease (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology (2006)[47]	• Levodopa does not appear to accelerate disease progression. • No treatment has been shown to be neuroprotective. • There is no evidence that vitamin or food additives can improve motor function in PD. • Exercise may be helpful in improving motor function • Speech therapy may be helpful in improving speech volume. • No manual therapy has been shown to be helpful in the treatment of motor symptoms, although studies in this area are limited. Further studies using a rigorous scientific method are needed to determine efficacy of alternative therapies.
Treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology (2006)[48]	• Entacapone and rasagiline should be offered to reduce off time (level A) • Pergolide, pramipexole, ropinirole, and tolcapone should be considered to reduce off time (Level B) • Apomorphine, cabergoline, and selegiline may be considered to reduce off time (Level C)

	- The available evidence does not establish superiority of one medicine over another in reducing off time - Sustained release carbidopa/levodopa and bromocriptine may be disregarded to reduce off time - Amantadine may be considered to reduce dyskinesia - Deep brain stimulation of the STN may be considered to improve motor function and reduce off time, dyskinesia, and medication usage - Preoperative response to levodopa predicts better outcome after DBS of the STN

European Academy of Neurology: Early (uncomplicated) Parkinson's disease (2011)[44]	No uniform proposal for initiating therapy in symptomatic patients. Initial therapy may include;
	
	- MAO-B inhibitors (e.g. selegiline or rasagiline)
	  - Effects more modest than levodopa but are easy to administer (one dose, once daily, no titration), and well tolerated (especially rasagiline).
	- Amantadine or an anticholinergic
	  - Effects more modest than levodopa are poorly tolerated in the elderly and are best restricted to young patients.
	- Levodopa is the most effective symptomatic antiparkinsonian. Long-term use often leads to motor complications. It is recommended in older patients who are more sensitive to neuropsychiatric adverse effects and less prone to motor complications. Early use of controlled-release formulations, do not delay motor complications
	- Dopamine agonist (pramipexole, piribedil, and ropinirole immediate- or controlled-release). Pramipexole and ropinirole have a lower risk of motor complications than levodopa. Lower class evidence, supports bromocriptine with no evidence suggesting they are less effective.
	  - Prevent motor complications but have less effect on symptoms and greater incidence of hallucinations, impulse-control disorders, somnolence, and leg edema, as compared with levodopa. Patients must be informed of these risks (e.g., excessive daytime somnolence is especially relevant to drivers).
	  - May be preferred for younger patients who are more prone to developing levodopa-induced motor complications.
	  - Ergot derivatives such as pergolide, bromocriptine, and cabergoline are not recommended as first-line medication because of the risk of fibrotic reactions.
	    - Pergolide*, bromocriptine, cabergoline and, with caution, other ergot derivatives, cannot be recommended as a first-line treatment for early PD because of the risk of valvular heart disorder

	○ Rotigotine is administered transdermally using a patch and ropinirole controlled-release (CR) once daily orally, as opposed to the other agonists that are administered orally three times a day.
	   ○ Subcutaneous apomorphine is not appropriate at this stage of the disease.
	   ○ The early combination of low doses of a dopamine agonist with low doses of levodopa is another option, although the benefits of such a combination have not been properly documented.
	
	Patients receiving dopaminergic therapy will develop worsening motor symptoms.
	 • Increase the dopamine agonist dose. Over 3-5 year it will lose efficacy.
	 • Switch between dopamine agonists
	 • Add levodopa
	
	For patients on levodopa
	 • Increase the levodopa dose
	 • Add a dopamine agonist (evidence not evaluated)
	 • Add a COMT-inhibitor to levodopa as status changes from non-fluctuating to fluctuating, especially in older patients and multimorbid patients of any age

European Academy of Neurology: Late (Complicated) Parkinson's disease (2011)[44]	**Symptomatic Control of Motor Complications - Motor Fluctuations: Wearing-off (end of dose akinesia, predictable ON-OFF)**
	 • Adjust levodopa dosing: Increase administrations to 4-6 doses daily
	 • Add catechol-O-methyltransferase (COMT) inhibitors or monoamine oxidase isoenzyme type B (MAO-B) inhibitors (selegiline, rasagiline) may reduce OFF time by 1-1.5 hr/day
	 • Add dopamine agonists.
	   ○ Non-ergot dopamine agonists are first-line compounds.
	   ○ other ergot agonists are reserved for second-line treatment, due to their association with lung, retroperitoneal, and heart valve fibrosis.
	   ○ Oral dopamine agonists are efficacious in reducing OFF time in patients experiencing wearing-off.
	   ○ Switch from standard to controlled-release levodopa. May also improve wearing-off and night-time akinesia.
	   ○ Add amantadine or an anticholinergic. In patients with disabling recurrent OFF symptoms that fail to improve further with the above-mentioned strategies, the addition of an anticholinergic (in younger patients), or amantadine, may improve symptoms in some cases
	
	Severe Motor Fluctuations
	 • When oral therapy fails: deep brain stimulation, subcutaneous apomorphine, intrajejunal levodopa/carbidopa enteric gel administered through percutaneous gastrostomy (PEG)

Dyskinesias: Peak-Dose Dyskinesia
- Reduce levodopa dose while increasing administration frequency
- Discontinue or reduce dose of MAO-B inhibitors or COMT inhibitors
- Add amantadine (200 to 400 mg/day). The benefit may last <8 months.
- Deep brain stimulation
- Add atypical antipsychotics, clozapine (12.5 and up to 200 mg/day) (caution: agranulocytosis and myocarditis) or quetiapine
- Apomorphine subcutaneous infusion can reduce levodopa requirement
- Intrajejunal levodopa infusion in patients with marked peak dose dyskinesia and motor fluctuations

Biphasic Dyskinesia: Consider deep brain stimulation or strategies for peak-dose dyskinesias.
- Increase size/frequency of levodopa dose (may increase dyskinesia)
- Larger less frequent levodopa for predictable response to plan ADL.
- Apomorphine and intrajejunal levodopa infusion can be tried

Off-Period and Early Morning Dystonias
- Wearing off strategies
- Additional levodopa or dopamine agonist therapy at night control of dystonia appearing during the night or early in the morning
- Deep brain stimulation
- Botulinum toxin

Freezing
- During the OFF and ON phases does not respond to dopaminergic therapy
- Off freezing strategy is the same as for wearing-off.
- ON freezing may respond to a reduction in dopaminergic therapy with possible worsening of wearing-off.

Symptomatic Control of Non-Motor Problems: Neuropsychiatric Complications
Treatment of Dementia in Parkinson's Disease (PD)
- Discontinue potential aggravators. Anticholinergics, amantadine, tricyclic antidepressants, tolterodine, oxybutynin and benzodiazepines
- Add cholinesterase inhibitors. Rivastigmine, donepezil, galantamine.
- Add or substitute with memantine if cholinesterase inhibitors not tolerated or lacking efficacy

Treatment of Psychosis in PD
- Control triggering factors. Treat infection and metabolic disorders, rectify fluid/electrolyte balance, treat sleep disorder.

• Reduce polypharmacy. Reduce/stop anticholinergic antidepressants, anxiolytics, sedatives.
• Reduce antiparkinsonian drugs. Stop anticholinergics, stop amantadine, reduce/stop dopamine agonists, reduce/stop MAO-B and COMT inhibitors, lastly, reduce levodopa. May worsen motor symptoms. (dopamine agonists have a higher psychosis-inducing potential than levodopa)
• Add atypical antipsychotics. Clozapine, insufficient evidence for quetiapine but safer.
• Add cholinesterase inhibitors, rivastigmine, donepezil

Treatment of Depression in PD
- Tricyclic antidepressants
- SSRIs produce less adverse effects than tricyclic antidepressants

Autonomic Dysfunction: Treatment of Orthostatic Hypotension in PD
- Avoid large meals, alcohol, caffeine at night, exposure to a warm environment, volume depletion, diuretics, antihypertensive drugs, tricyclic antidepressants, nitrates, alpha-blockers used to treat urinary disturbances related to prostatic hypertrophy.
- Levodopa, dopamine agonists, and MAO-B inhibitors may also induce orthostatic hypotension.
- Increase salt intake (symptomatic orthostatic hypotension), tilt head of bed (30°–40°), waist-high elastic stockings and/or abdominal binders, exercise as tolerated, counter measures (leg crossing, toe raising, thigh contraction, bending at the waist), for post-prandial effects recommend small meals
- Drug Therapy
  - Midodrine
  - Fludrocortisone

Pharmacology

MAO Inhibitors

Monoamine oxidase is an intracellular, mitochondrial-bound, enzyme class that catalyzes oxidative deamination of monoamine and indolamine neurotransmitters in the CNS.[4,5,49] MAO regulates the content of monoamines in the CNS, thereby playing a significant role in regulating neurotransmission, mood, emotions and other MAO regulated brain functions.[2] Some byproducts of MAO activity are neurotoxic (hydrogen peroxide, ammonia and aldehydes) and produce adverse mitochondrial and neurodegenerative effects.[5,42] MAOs also catabolize amines of food and drug origin while gastrointestinal MAO inhibits the absorption of exogenous amines like tyramine. Use of MAOIs prevents tyramine degradation, allowing for absorption of tyramine. Ingestion of large tyramine loads in the presence of an MAOI may result in the displacement of norepinephrine from synaptic vesicle storage resulting in hypertension.[1,49-52]

In humans there are two MAO isoenzymes, MAO-A and MAO-B.[1,42,51,53,54] MAO-A is found in the brain, gastrointestinal tract and liver. MAO-A has substrate- specificity for norepinephrine, serotonin, epinephrine, normetanephrine, octopamine, tyramine and dopamine.[1,4,49 51] MAO-A modulation of serotonin is associated with depression and MAO-A

inhibitors are effective antidepressants.[54] MAO-A inhibitors are currently unavailable in the US.[4] MAO-B is located in the brain and platelets. MAO-B is substrate specific for phenethylamine, benzylamines, phenelethylamine, N-methyhistamine, tyramine and dopamine.[1,49,51]

MAOIs can be differentiated based on enzyme specificity, binding or chemical structure. Isocarboxazid, phenelzine and tranylcypromine are non-specific inhibitors of MAO, exhibiting irreversible binding to both MAO-A and MAO-B.[1,49,55] Selegiline and rasagiline demonstrate irreversible binding to MAO-B at low doses, with a loss of specificity at higher doses. Specifically, selegiline becomes a nonspecific MAOI at antidepressant dosages.[1]

Due to irreversible enzyme inhibition, the MAOIs exert effects for the duration of the enzyme lifespan. Although plasma half-lives are in the range of 1-4 hours, the clinical activity of these medications persists up to 3 weeks as 7-14 days are required to regenerate MAO enzymes.[1,4,49,53]

Hydrazine MAOIs are derivatives of iproniazid.[2] Use of the hydrazine compounds may be associated with hepatotoxicity.[1] Metabolism of the non-hydrazine MAOIs produces low quantities of amphetamine, although the drugs do not typically produce euphoria and are not habit forming.[1,2]

Mechanism of Action

Antidepressant: The antidepressant activity of the MAOIs results from higher concentrations of synaptic monoamines, however, the 2-4 week lag in antidepressant effects suggests that late adaptive mechanisms are the primary mechanism of antidepressant activity.[2,4,53] MAOIs downregulate and reduce the number of $\alpha 1$, α-2, β-adrenoreceptors, and $5HT_1$, $5HT_2$ and serotonergic binding sites within the central nervous system.[1,2,4,53]

Parkinson's Disease: The mechanism of activity of selegiline and rasagiline in the treatment of Parkinson's disease includes reductions in oxidant and nitrosative stress, mitochondrial membrane stabilization, cellular antioxidant upregulation, apoptotic activity and increased neurogenesis and apoptotic activity.[56] Of theoretical debate is whether the neuroprotective activity of selegiline is reduced by the neurotoxic effects of its metabolite, L-amphetamine.[56] Administration of selegiline and rasagiline at Parkinson's disease doses results in selective MAO-B inhibition. Parkinson's doses of MAO-B inhibitors does not inhibit MAO-A activity in the gut and the risk of tyramine reactions are low, although one case of hypertensive crisis has occurred when selegiline was used in combination with a sympathomimetic medication.[55]   At higher, antidepressant doses, MAO-A inhibition may occur and the risk of a tyramine reaction increases.

Pharmacokinetics

The MAOIs have poorly defined pharmacokinetic parameters.[1,57] The agents are rapidly and well absorbed.[58] MAOIs are highly protein bound, undergo extensive first-pass hepatic metabolism and are eliminated with half-lives ranging from 1-4 hours.[1,31] Phenelzine undergoes acetylation. Differences in acetylator phenotype may affect phenelzine elimination rates.[31] MAO enzyme inhibition is irreversible, resulting in pharmacological effects, side effects and the

potential for drug interactions until MAO is regenerated, typically 7-14 days.[58,1,31] See **Table 5** for a comparison of the MAOIS pharmacokinetics.

Table 4: Pharmacokinetics of Tricyclic (and Tetracyclic) Antidepressants

	Absorption	Distribution	Metabolism Active Metabolite	Excretion	Elimination Half-life
Isocarboxazid	Onset of Action: 1 to 6 weeks Time to peak MAO inhibition: 5 to 10 days				
Phenelzine	Well absorbed Tmax: 43 minutes Onset of Action: ≥ 4 weeks Duration: 2 weeks after d/c		Monoamine oxidation and acetylation Inactive: phenylacetic acid, parahydroxyphenylacetic acid and N(2)-acetylphenelzine	73% as metabolites	11.6 hours
Rasagiline	BA: 36% Tmax: 1 hour Duration: 7 days after d/c	Vd 87L PB: 88-94%	CYP1A2; N-dealkylation and/or hydroxylation Inactive: 1-aminoindan	Renal: 62% Fecal: 1%	3 hours
Selegiline	BA: Higher with orally disintegrating tablet Tmax: Oral tablet 40 to 90 minutes Orally disintegrating tablet: 10-15 minutes Duration: 24-72 hours Onset of action: 1 hour Food effects: Oral tablet/capsule: BA increased 3-4-fold Orally disintegrating tablet: AUC and Cmax decreased 60% Transdermal:	PB: 90% Oral disintegrating tablet: 85% Transdermal: 90%	CYP2B6, CYP3A4, and CYP2A6 (minor) Active: N-desmethylselegiline Inactive: amphetamine, methamphetamine	Oral Products: Renal: Major Fecal: Minor Transdermal: Renal: 10% Fecal: 2%	Oral: 10 hours Transdermal: 18 to 25 hours

	Absorption	Distribution	Metabolism Active Metabolite	Excretion	Elimination Half-life
	BA: 25-30% over 24 hours				
Tranylcypromine	Absorption: Rapid Cmax: 1.5 hours Tmax: 0.67 to 3.5 hours Onset of action: 2 days to 3 weeks Duration: 10 days after d/c	Vd: 3.09 L/kg			2.5 hours

Special Populations[6-8] *(See Table 6)*

Pediatrics: Use in children is not established. Isocarboxazid is labelled for use in adolescents ≥ 16 years of age.

Geriatrics: Therapy with oral phenelzine or selegiline should be initiated at a lower dosage to minimize adverse effects.

Pregnancy/Breast Feeding: Isocarboxazid, rasagiline and selegiline are categorized by the FDA as pregnancy category C while phenelzine and tranylcypromine have no US pregnancy class assignment and a recommendation to consider the risk-benefit of therapy. Prescribers are encouraged to enroll every pregnant woman receiving these agents in the National Pregnancy Registry for Antidepressants (https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/). It is unknown whether these agents cross into breast milk. A risk-benefit assessment for use during breastfeeding is recommended.

Hepatic impairment: Isocarboxazid and tranylcypromine are contraindicated in patients with a history of liver disease or abnormal liver function tests. Rasagiline and selegiline should be used cautiously and at lower doses with mild to moderate hepatic impairment and avoided with more significant hepatic dysfunction. Data is lacking for phenelzine and if prescribed, caution is advised.

Renal impairment – MAOIs may accumulate in the presence of renal dysfunction. Caution is recommended in mild to moderate renal dysfunction and these agents are best avoided in severe renal impairment.

Table 5: Special Populations

	Renal	Hepatic	Pregnancy*	Excretion in Breast Milk	Pediatric (Dosing see Table 1)	Geriatric
MAO Inhibitors						
Isocarboxazid	Caution in mild-to-moderate impairment (accumulation) Contraindicated in severe impairment	Contraindicated with abnormal LFTs or history of liver disease	C	Unknown Consider the risk/benefit of therapy	Age < 16 years: Not established	Usual adult dosing
Phenelzine	No recommendation	No information	**	Unknown Consider the risk/benefit of therapy	Not established	Begin with lower doses: 15 mg in the morning; gradually titrate to minimize adverse effects Max: 60 mg daily
Rasagiline	Mild to moderate impairment: No adjustment necessary Severe impairment: Not studied	Child-Pugh score 5 to 6 (mild impairment): Max dose is 0.5 mg once daily Child-Pugh score 7 to 15 (moderated to severe impairment): Not recommended	C	Unknown Consider the risk/benefit of therapy	Not established	Use adult dosing
Selegiline	Tablets/capsules: Use with caution (not studied) Orally disintegrating tablet: • Severe impairment (CrCl <30 mL/minute) or ESRD: Use is not recommended Transdermal:	Tablets/capsules: Use with caution (not studied) Orally disintegrating tablet: • Child-Pugh class C (severe impairment) Use is not recommended. Transdermal:	C	Unknown Not recommended	Not established	Tablet/capsule: ≤5 mg daily with levodopa to decrease dopaminergic side effects day Orally disintegrating tablet: Use adult dosing Transdermal: 6 mg/24 hours

28

	Renal	Hepatic	Pregnancy*	Excretion in Breast Milk	Pediatric (Dosing see Table 1)	Geriatric
	• eGFR <15 mL/minute/1.73 m2: Not studied	• Child-Pugh class C (severe impairment) Not studied				
Tranylcypromine	No recommendations	Contraindicated with abnormal LFTs or history of liver disease	**	Unknown Not recommended	Not established	Initiate therapy with lower doses to minimize adverse effects

Key: *-Pregnant women, 18 to 45 years of age, receiving antidepressants are encouraged to enroll in the National Pregnancy Registry for Antidepressants (NPRAD) as early in pregnancy as possible; **-No US assignment, inconclusive results, consider risk-benefit of therapy; LFTs-liver function tests; ESRD-end-stage renal disease

Methods

A literature search was conducted to identify articles addressing each key question, searching the MEDLINE database, EMBASE, the Cochrane Library and reference lists of review articles. For the clinical efficacy section, only clinical trials published in English and indexed on MEDLINE or EMBASE, evaluating efficacy of the MAOI antidepressants are included. Trials evaluating the agents as monotherapy or combination therapy where adjunctive medications remained constant throughout the trial are included. Non-comparative and placebo-controlled trials and trials comparing monotherapy with combination regimens are generally excluded.

Evidence

Evidence for MAOIs was for a number of indications, including depression, treatment-resistant, chronic, atypical, recurrent and elderly depression, Parkinson's disease, Parkinson's fatigue and for the non-labelled indications bulimia nervosa, social anxiety disorder and smoking cessation. MAOIs are the oldest class of antidepressant medications. Most trials for the treatment of depression were performed prior to modern methodologic standards. Most MAOI studies were efficacy and not effectiveness trials, limiting extrapolation to the average patient. Patients with comorbidities were most often excluded from trials. Additionally, antidepressant trials are confounded with a significant placebo effect.[59] Overall, methodological deficiencies were common and direct comparative evidence remains overall lacking.

Depression: A Systematic Review and meta-analysis[1] evaluated the use of MAOIs in the treatment of depression. Fifty-five randomized, controlled trials were identified. Meta-analysis of intent-to treat (ITT) samples in outpatient populations found each of the MAOIs performed well (phenelzine 57.9% ± 4%; isocarboxazid 60.1% ± 7.1%; tranylcypromine 52.6% ± 12.4%). The efficacy advantage vs placebo in the outpatient setting was highest for isocarboxazid (41.3% ± 18%, 3 studies) followed by phenelzine (29.5% ± 11.1%, 9 studies) and tranylcypromine (22.1% ± 25.4%, 3 studies) however, large intra-group variability precluded a finding of statistical significance. The efficacy advantage vs placebo for inpatients found phenelzine (22.3% ±30.7%) more effective than isocarboxazid (15.3% ± 12.6%). Comparisons with tricyclic antidepressants found the TCAs more effective than MAOIs in the inpatient setting and for severe depression. MAOIs outperformed TCAs in the outpatient setting particularly when atypical symptomatology (e.g. phobic or panic anxiety, overeating, oversleeping weight gain) was present. MAOI therapy was effective in 50% of TCA-resistant patients and resulted in a 70% response rate. MAOIs remained effective over the maintenance and continuation phases of therapy with 80-90% continuing to respond at 6 months.

Young et al[60] compared treatment with trimipramine, phenelzine, isocarboxazid or combination therapy in mild to moderately depressed outpatients (N=135). No difference was found on efficacy measures for phenelzine or isocarboxazid. Davidson et al[61] found imipramine and phenelzine were equally effective in the treatment of 43 depressed inpatients. Phenelzine was noted to increase hostility while imipramine reduced both hostility and paranoia.

> Assessment: MAOI therapy may be preferred in patients with atypical depression. No differences between MAOIs in outpatient therapy have been identified. Inpatient therapy with MAOIs may be less effective than TCAs with phenelzine superior to isocarboxazid. MAOIs are effective in TCA-resistant depression. Clinically significant MAOI antidepressant effects persist for at least 6 months.

Treatment Resistant Depression: Birkenhager et al[62] compared phenelzine and tranylcypromine in 77 patients with treatment-resistant major depressive disorder who failed a tricyclic antidepressant or fluvoxamine. Both drugs produced similar rates of ≥ 50% reduction in HAM-D scores. Severe side effects (dizziness, agitation, insomnia) occurred at a similar rate (~20%) with both drugs.

In two small studies, Thase et al[63,64] found MAOIs, tranylcypromine and phenelzine, effective in imipramine-resistant depression or anergic bipolar depression (significance at least $p<0.05$ for various measures of depression in both studies).

McGrath et al[65] evaluated the response of chronically depressed outpatients who failed initial therapy with phenelzine or imipramine to crossover therapy with the alternative medication. Phenelzine demonstrated statistical superiority over imipramine in reducing the symptoms of depression (55% vs 27%; $p=0.01$).

Assessment: Phenelzine and tranylcypromine are effective and do not differ in treatment-resistant depression. MAOIs may be superior to TCAs but additional evidence is needed.

Depressive Recurrence: Stewart et al[66] compared the ability of imipramine and phenelzine to prevent a recurrence of depression in patients stabilized on therapy for 6 months. Recurrence rates were lower with phenelzine than imipramine (23% vs 41%). More patients receiving phenelzine were chronically depressed and the study was hampered by a lack of power to detect a difference.

Assessment: Further studies are needed to define the ability of MAOIs and TCAs to prevent depressive recurrences.

Chronically Depressed: Stewart et al[67] performed a subset analysis of a previous trial[66] comparing phenelzine and imipramine therapy in chronically depressed patients (N=153) most of whom (80%) met criteria for atypical depression. Response rates were higher with phenelzine than imipramine (RR 70%; $\chi 2 = 5.96$; $p=0.015$), while imipramine performed statistically better than placebo ($p=0.002$). These results may reflect the fact that MAOIs perform better than TCAs in the setting of atypical depression.[68]

Assessment: Included for place-in-therapy. MAOIs may be useful in chronically depressed patients although evidence is insufficient to find MAOIs superior to TCAs (i.e. imipramine). Most studies were very small and predated modern study design standards.

Depression in the Elderly: A Cochrane review[69] evaluated the benefit of antidepressant therapy in the depressed elderly. Seventeen trials of 1326 participants compared treatment with MAOIs, TCAs or SSRIs or placebo therapy. Efficacy was assessed with a fixed effects model that found all three antidepressant classes more effective than placebo therapy [OR, TCAs 0.32 (95% CI: 0.21-0.47); SSRIs; 0.51 (95% CI: 0.36-0.72); MAOIs 0.17 (95% CI: 0.07-0.39)]. Evidence was insufficient to compare specific agents within or between classes. Georgotas et al[70] compared nortriptyline and phenelzine in the maintenance therapy of elderly depressed patients (N=51). Phenelzine was found superior to nortriptyline and placebo in preventing recurrences (13.3% vs 53.8% vs 65.2%, respectively) over 1 year.

Assessment: No difference has been found between MAOIs, TCAs, atypical antidepressants or SSRIs in treating the depressed elderly. MAOIs (i.e. phenelzine) may be more effective than TCAs (i.e. nortiptyline) in preventing depressive recurrences.

Depression with Atypical Symptoms: A meta-analysis[71] evaluated the efficacy of MAOs, SSRIs and TCAs in the treatment of depression with atypical features. Rigorous inclusion criteria resulted in inclusion of only eight trials of 670 participants, that allowed for 11 comparisons. Placebo-controlled trials demonstrated significant improvement in Hamilton Depression Rating Scale (HAM-D) or Montgomery-Asberg Depression Rating Scale (MADRS) with MAOIs (effect size, d=0.45; 95% CI 0.352-0.605). Little difference was found between MAOIs and SSRIs (effect size d=0.02; (95% CI -0.10, 0.14). MAOIs were superior to TCAs (effect size, d=0.27; 95% CI 0.16-0.42). Clinical symptoms responded significantly better with MAOIs than TCAs. Interpretation of this data is limited by the small sample sizes and lack of validation of the HAM-D tool for atypical symptomatology.

Assessment: Included for place in therapy. MAOIs appear to perform better than TCAs in atypical depression.

Parkinson's Disease: Three Cochrane Reviews evaluated the use of MAO-B therapy in Parkinson's disease. Two evaluated treatment in early Parkinson's disease. The first review[72] included 11 trials involving 2514 participants in which selegiline was the MAO-B studied in most trials. MAO-B therapy was not associated with increased mortality. Overall, MAO-B therapy did not improve disability or delay disease progression. MAO-B therapy did produce a weak, short-term levodopa-sparing effect, reduced motor fluctuations (25%) but did not improve dyskinesias. The most common adverse event was nausea and all events were mild. A second Cochrane Review[73] compared dopamine agonists, levodopa and selegiline in early Parkinson's disease. Included were 2 trials of 593 participants. MAO-B therapy was not associated with increased mortality. MAO-B therapy reduced motor fluctuations more than levodopa therapy. Selegiline treatment more commonly resulted in the need for add-on therapy than other agents. Dopamine agonists were associated with more withdrawals due to adverse events than MAO-B therapy. The third review[74] evaluated adjunctive therapy in Parkinson's disease. Dopamine agonists were more efficacious than MAO-B or COMT medications in reducing off-time, reducing levodopa dosage requirements and clinician rated disability scores. MAO-B and COMT therapy yielded similar outcomes. Tolerability was lower with dopamine agonists than other agents. Adverse event rates and dyskinesia rates were higher with dopamine agonist therapy.

Assessment: Included for Assessment: MAO-B agents do not appear to increase mortality in Parkinson's disease patients. No comparative trials have evaluated selegiline vs rasagiline. Among other therapies, MAO-B therapy does not appear more efficacious although tolerability may be better.

Parkinson's Disease Fatigue: A Cochrane Review[75] evaluated treatment of fatigue in Parkinson's disease (N=1817). Interventions included levodopa-carbidopa, memantine, rasagiline, caffeine, methylphenidate, modafinil, doxepin or placebo. Three of 11 trials required the presence of clinically significant fatigue for inclusion. Evidence found that only rasagiline reduced or slowed the progression of fatigue. One study of 1176 participants found rasagiline vs placebo resulted in a standard mean difference in fatigue (SMD) of -0.27 (95% CI -0.39, -0.16, I2=0%). Treatments

were well tolerated although levodopa-carbidopa treatment was associated with significant nausea.

> *Assessment: Included for place in therapy. Rasagiline appears to have a place in the treatment of PD fatigue. No other agent demonstrated efficacy. Doxepin may reduce the impact of fatigue on ability to perform the activities of daily living (ADL) but further evidence is needed.*

Bulimia Nervosa: A Cochrane Review[76] evaluated the effects of antidepressants for the treatment of bulimia nervosa in 19 placebo controlled trials including TCAs (6 trials; imipramine, desipramine, amitriptyline), SSRIs (5 trials; fluoxetine), MAOIs (5 trials; phenelzine, isocarboxazid, moclobemide, brofaromine) and miscellaneous agents (mianserin, trazodone, bupropion). Treatment with a single antidepressant was more efficacious than placebo in reducing binge episodes with a modest RR 0.87 (95% CI 0.81-0.93; p<0.001). The response to TCAs was a RR of 0.86 (95% CI 0.70 to 1.07) to MAOIs, a RR of 0.81 (95% CI 0.68 to 0.96) and to SSRIs a RR of 0.89 (95% CI 0.76 to 1.03). The dropout rate was highest with TCAs and lowest with fluoxetine. Evidence was insufficient to determine a difference between the efficacy of the various classes of antidepressants.

> *Assessment: MAOIs, SSRIs and TCAs are effective in reducing binge episodes, although comparative data is lacking.*

Social Anxiety Disorder: A Cochrane Review[77] evaluating antidepressant medications for social anxiety disorders found phenelzine performed well in comparison to SSRIs. Evidence from 37 trials (N=5264) analyzed changes in Clinical Global Impressions scale and Liebowitz Social Anxiety scales. SSRIs and MAOIs were significantly more effective than placebo. Dropout rates were higher with MAOI therapy than SSRI therapy (Risk Ratio 1.05 [0.88, 1.25] vs 1.13 [0.46, 2.77], no *p* value was reported). Kosten et al[78] found phenelzine improved intrusion but not avoidance symptoms associated with PTSD more than imipramine (44% vs 25%).

> *Assessment: MAOIs may efficacious in the treatment of PTSD; further studies are needed.*

Smoking Cessation: One Cochrane review[79] of pharmacotherapy for smoking cessation included five selegiline trials Selegiline was found ineffective in smoking cessation.

> *Assessment: MAOIs should not be used for smoking cessation.*

Evidence Summary

Evidence is insufficient to identify differences in efficacy between MAOIs. A review of the evidence finds that comparative evidence between MAOIs or MAO-Bs is scarce. In the treatment of depression, MAOI efficacy appears to persist for at least 6 months. Available evidence suggests that phenelzine may be superior to isocarboxazid in inpatient treatment of depression while no difference was found between phenelzine and tranylcypromine in treatment-resistant depression. Evidence finds that compared to TCAs, MAOIs may be especially useful in the treatment of atypical depression. Although efficacious in the treatment of bulimia nervosa and social anxiety disorders comparative evidence is unavailable. MAOIs should not be used for smoking cessation. There are no comparative trials with selegiline transdermal therapy for depression. Rasagiline was found efficacious in the treatment of Parkinson's disease fatigue

although comparative evidence is unavailable. Evidence found no increase in mortality with use of MAO-B agents in the treatment of Parkinson's disease. Comparative evidence is lacking for MAO-B therapies in Parkinson's disease. MAO-B therapy was not more effective than other anti-Parkinson therapies but may be better tolerated.

Safety

Black Box Warnings[6-8]

　　All MAOIs, except rasagiline which is not labelled for use in depression, carry a Black Box warning for an increased risk of suicidal thinking and behavior in children, adults and young adults (18-24 years of age) with major depressive disorder and other psychiatric disorders.[7,8,80] Evidence has found that the risk of suicide attempts or completed suicides is not different with any specific class of antidepressant in adults or children and adolescents.[81,82]

Contraindications[6-8]

　　Phenelzine, isocarboxazid and tranylcypromine: Sensitivity to the drug, pheochromocytoma, CHF, history of liver disease, severe renal impairment or disease, suspected cerebrovascular or cardiovascular disease, hypertension, history of headache, current use of other MAOIs, TCAs, carbamazepine, cyclobenzaprine, bupropion, SSRIs, SNRIs, buspirone, guanethidine, sympathomimetic or related drugs (methyldopa, levodopa l-tryptophan, l-tyrosine, phenylalanine, reserpine) dextromethorphan, anesthetic agents, general anesthesia, spinal anesthesia CNS depressants, antihypertensive medications, thiazides, tryptophan, caffeine, aged cheese with high tyramine content, cocaine, sympathomimetic vasoconstrictors.[2]

　　Selegiline, rasagiline: Concomitant use of other MAOI or various other serotonergic medications (e.g. meperidine, methadone, tramadol, dextromethorphan, cyclobenzaprine, St John's wort). Allow 14-day washout period before starting another serotonergic medication. Bizarre behaviors have been observed when rasagiline was used with dextromethorphan.

Warnings/Precautions[6-8]

　　MAOIs may cause clinical worsening of depression with suicide risk. Patients should be screened for bipolar disorder to prevent MAOI-induced precipitation of a mixed/manic episode. Bipolar and hyperkinetic patients may develop hypomania. Due to risk of serious adverse reactions, these agents are not recommended as first-line therapy for depression. Populations at an increased risk of hypertensive crisis or hyperthermia. include the elderly, debilitated patients and those with hypertension, cardiovascular or cerebrovascular disease. Serotonin syndrome, sometimes fatal, may occur with concomitant use of SSRI antidepressants. A washout period is required after discontinuing an SSRIs or TCAs before initiating MAOI therapy. Rapid withdrawal of an MAOI may be associated with nausea, vomiting and malaise. Further, a rare withdrawal reaction may occur 24-72 hours after discontinuing MAOI therapy with vivid nightmares, agitation, psychosis and convulsions. Tranylcypromine and isocarboxazid may worsen anxiety and agitation. Slow uptitration of doses and divided dosing may be required in patients experiencing postural hypotension. Hypoglycemia due to increased insulin sensitivity may occur in patients receiving hypoglycemic medications. MAOIs lower the seizure threshold and a 48-hour discontinuation is recommended before metrizamide myelography. Patients should be monitored clinically monitor for signs and symptoms of hepatotoxicity. Anginal pain is

suppressed and sensitivity to pressors is increased in hyperthyroid patients. Accumulation may occur in the presence of renal or hepatic dysfunction. Very rarely, drug dependence has been reported.

Adverse Effects[6,7]

MAOIs produce early and late adverse effects. Early adverse effects include orthostatic hypotension, dizziness, drowsiness, headache, insomnia, mydriasis, nausea and piloerection.[2,4] Phenelzine is the most sedating of the agents. Most of the early adverse effects are easily managed by slow dosage uptitration, divided dosing, increased fluid intake and bedtime dosing. Late adverse effects include carbohydrate craving, weight gain, edema, hypoglycemia, hypomania, myalgia, myoclonus, paresthesias, tremor, blood dyscrasias, urinary retention and sexual dysfunction.[1,2,4] Paresthesias may be prevented with pyridoxine supplementation.[1] Orthostatic hypotension may also occur as a late effect, 3 to 4 weeks after therapy is initiated.[49] Phenelzine and isocarboxazid produce more hypotension, weight gain, sexual dysfunction and urinary retention than other agents,[49] whereas edema is more common with tranylcypromine.[2] Amoxapine use has produced tardive dyskinesia while maprotiline is associated with an increased risk of grand-mal and other seizures. A number of side effects associated with MAOI use are plasma-level dependent (e.g. orthostasis) and reversible within hours after drug discontinuation.

Transdermal selegiline is associated with application site reactions, headache, diarrhea, dyspepsia, sinusitis, hallucinations, insomnia, dry mouth, orthostatic hypotension, somnolence, falling asleep during activities of daily living, pharyngitis, psychotic-like behavior, issues of impulse control and serotonin syndrome. Therapy discontinuations in clinical trials occurred only due to application site reactions.[55] Transdermal selegiline is not associated with sexual dysfunction. A meta-analysis of four short-term trials involving 789 participants found transdermal selegiline (6 mg/24 hours) was not different than placebo for measures on the Medex Sexual Dysfunction subscale for both men and women.[83]

Evidence evaluating the safety of rasagiline in Parkinson's disease was presented in a review[56] that evaluated the rasagiline clinical trials, post-hoc and sub-analysis data. Rasagiline did not produce cardiovascular (orthostatic hypotension) or psychiatric effects (hallucinations) in patients younger than 65 years of age. Older patients experienced an increased incidence of depression, hallucinations and orthostatic hypotension.

A number of serious, rare adverse event are associated with use of nonspecific MAOIs. Hepatotoxicity is associated with use of the hydrazine MAOIs (phenelzine and isocarboxazid). Elevations of aspartate transaminase (AST) and alanine transaminase (ALT) occurred in 3 to 5% of patients. Monitoring liver function is not necessary unless a patient presents with symptoms or signs of hepatotoxicity.[1,2] Transient, self-limited hypertension has occurred unrelated to diet or drug interactions and may range from asymptomatic hypertension to hypertensive crisis.[4]

Hypertension is more common with tranylcypromine.[49] Phenelzine and isocarboxazid produce less hypertension.[1,49] It was estimated in 1988, that hypertensive crisis occurs with an incidence of approximately 20%.[1] Although hypertension is reversible, stroke or death may occur in vulnerable patients.[1] Limiting dietary tyramine, sympathomimetics and vasoactive amines should virtually eliminates the risk of hypertensive crisis, however, it is suspected that a risk of 5% per patient-year of therapy is possible.[1]

Hypertensive Crisis-Tyramine Reactions : Hypertensive crisis may occur when an MAOI is ingested with cheese, fermented foods or other high-content tyramine foods.[4,84] Within minutes of eating a tyramine-rich foodstuff the reaction begins with symptoms including a severe, pulsating headache, palpitations, sweating, blurred vision, chest pain, shortness of breath, flushing, stiff neck and nausea.[49] Serious sequelae include the risk of stroke.[49]

MAOIs inhibit the metabolism of tyramine. Absorbed tyramine displaces norepinephrine from intracellular, sympathetic nerve vesicles resulting in precipitous elevations of blood pressure.[49,84] Hypertensive reactions are more common with non-hydrazine than hydrazine MAOIs, although the reaction may occur with higher doses of hydrazine MAOIs (i.e. phenelzine).[84,85]

A tyramine content of less than 6 mg per serving is generally regarded as safe.[4,84,86-91] A tyramine dose of 10 mg may produce a moderate reaction,[2] whereas a tyramine intake of 20 mg may produce a serious rise in blood pressure.[84] Death is extremely rare, but has occurred in 0.01% to 0.02% of patients receiving tranylcypromine.[2] Foods to avoided include aged cheeses and meats, banana peels, fava and other broad beans, spoiled meats, sauerkraut, soybean products, tap beer and Marmite concentrated yeast. Wine and bottled beer may be consumed in moderation and there is no need to limit parmesan or mozzarella cheese intake.[86] Pizza Hut and Domino's pizzas have been specifically tested and found safe to eat while on MAOI therapy.[89]

Selegiline is available in a transdermal patch which limits enterohepatic MAO inhibition.[55,92] At selegiline patch doses of 6 mg/24 hours, tyramine restriction is unnecessary.[55,92] However, higher selegiline doses may require dietary modifications. Overall, the tyramine restricted diet required for safe use of MAOIs is not overly burdensome and should not limit use of these potent antidepressants.

Tolerability:

A retrospective, database analysis of 75 managed care plans (covering 55 million persons) assessed antidepressant tolerability.[93] A change in therapy occurred more often with TCA or MAOIs (40.1%) than with SSRIs/SNRI (21.2%) or newer antidepressants (18.3%). Adherence rates demonstrated a similar trend (12.4% vs 29.3% vs 33.6%, respectively). Treatment with TCA/MAOIs for 6 months was associated with significantly higher odds for all-cause hospitalizations and costs.

Mortality:

A study performed in early Parkinson's disease documented an increase in mortality with use of selegiline. The United Kingdom trial compared the addition of selegiline or dopa-decarboxylase inhibitor therapy to levodopa in 520 patients with early Parkinson's disease. The study was terminated early due to an interim analysis finding of increased mortality between groups. After adjustment for age, sex, level of disability before treatment, duration of Parkinson's disease, and year of entry to the trial, the selegiline arm mortality hazard ratio was 1.57 (95% confidence interval 1.07 to 2.31).[94] Although of concern initially, subsequent meta-analysis have disproven this risk.[95]

Toxicity:

MAOI toxicity is a result of abnormalities in cardiac conduction that may result in severe hypotension and vascular reactivity. Intensive hospital monitoring over 3-4 days may be required as the drug is eliminated from the body.[1]

Drug Interactions:

MAOIs can impair the oxidative degradation of other medications. This effect is augmented with concomitant vasoactive amines, cocaine, caffeine, xanthines, decongestants, stimulants and epinephrine.[1,4]

MAOIs inhibit CYP2C19 and may increase the concentrations of medications metabolized by these enzymes (e.g. citalopram, escitalopram, omeprazole, sertraline).[4] Phenothiazine antipsychotics increase serum levels of tranylcypromine. Due to the long pharmacodynamic half-life resulting from irreversible enzyme inhibition, a washout period of approximately 14 days is recommended before initiating therapy with an interacting medication (e.g. serotonergic medications).[4] Likewise, before initiating an MAOI, discontinuation of interacting medications and a waiting period of 4-5 half-lives of the discontinued agent should be observed. Long-acting, interacting, serotonergic medications like fluoxetine may require a waiting period of 4-5 weeks.[4]

Drugs that are best avoided in combination with an MOAI, include stimulants (e.g. dextroamphetamine, methylphenidate), meperidine, L-tryptophan and indirect-acting sympathomimetics.[8] Dextromethorphan should not be used in high doses. Direct sympathomimetics and buspirone should be avoided, however, if they must be used, close monitoring is recommended. Patients receiving hypoglycemic medications require blood sugar monitored to avoid severe hypoglycemic complications. Concomitant carbamazepine, cyclobenzaprine and TCAs are less likely to produce a significant drug interaction, however, caution is recommended when used in combination with an MAOI. Caution should be exercised when combining a MAOI with beta-blockers, disulfuram, antihypertensives, rauwolfia alkaloids, sulfonamides, selective 5-HT_1 receptor agonists or tramadol. SSRIs should not be used with an MAOI unless under the care of a specialist.[1,96]

In making changes to antidepressant therapy, it is important to consider the time required to for monoamine enzyme regeneration. A 2-3 week washout period should be observed if switching from an SSRI or TCA to MAOI, remembering that due to the very long half-life of fluoxetine a 5-week delay is necessary.[2] Changes to alternative MAOIs require at least a 1-week washout period.[8] A waiting period of 14 days is recommended between apraclonidine and MAOIs.[8]

Rasagiline serum concentrations are affected by CYP1A2 inducers (e.g. omeprazole) and inhibitors (e.g. ciprofloxacin) resulting in lower and higher rasagiline serum levels, respectively.[7,56,80] Levodopa dyskinesias may be worsened by rasagiline although clinical trials did not allow for the usual practice of levodopa dose reduction when dyskinesias developed.[56] Additional long-term studies are required to determine whether rasagiline increases dyskinesias in combination with levodopa therapy.[56] Tyramine reactions have not been reported with rasagiline therapy.[97] The safety of rasagiline and serotonergic therapies has not been adequately studied, however, a life-threatening case of serotonin syndrome was reported when selegiline was combined with meperidine and it is expected that the risk is similar with rasagiline.[56]

Serotonin Syndrome: Serotonin syndrome usually results from drug interactions with other serotonergic agents, however, it has been reported with MAOI monotherapy.[4] Combining MAOIs with other serotonergic medications (e.g. meperidine, SSRIs, tramadol, chlorpheniramine, cyclobenzaprine, triptan medications, divalproex, TCAs, dextromethorphan, cocaine, ergot alkaloids, fentanyl, linezolid, lithium, L-tryptophan, methadone, methamphetamine, methylene blue, metoclopramide, mirtazapine, ondansetron, pentazocine, St John's wort) may result in serotonin syndrome.[98-101] The syndrome includes neuromuscular hyperactivity (tremor, clonus, myoclonus, hyperreflexia, pyramidal rigidity), autonomic hyperactivity (diaphoresis, hyperthermia, tachycardia, tachypnea) and altered mental status (agitation, excitement, confusion) resulting from hyperstimulation of the brainstem $5HT_{1A}$ receptors.[100,101]

Clinically significant interactions are most common when combined medications increase serotonin by different mechanisms.[99,100,101] Medications increasing serotonin by a different mechanism than MAOIs, include SSRIs and linezolid.[99] Some phenylpiperidine opioids (meperidine, tramadol, methadone, fentanyl and dextromethorphan) exhibit weak SRI activity and have produced dose-dependent serotonin toxicity with some fatalities.[98] The use of serotonin releasing agents such as ecstasy (MDMA; 3,4-methylenedioxymethamphetamine) with MAOIs has the potential for significant toxicity and death.[99] The interaction between MAOIs and TCAs is most significant for clomipramine.[49]

Summary:

MAOI medications have been available for use in the treatment of depression for over 60 years although they are rarely used due to the potential for serious adverse effects. By the 1970s, MAO-B which degrades dopamine, was found in high concentration in the basal ganglia of the brain and MAO-B inhibition were identified and developed for use in the treatment of Parkinson's disease, a disease of brain dopamine deficiency.

Evidence is insufficient to identify differences in efficacy between MAOIs. A review of the evidence finds that comparative evidence among MAOIs or MAO-Bs is scarce. In the treatment of depression, MAOI efficacy appears to persist for at least 6 months. Available evidence suggests that phenelzine may be superior to isocarboxazid in the treatment of inpatient depression, while no difference was found between phenelzine and tranylcypromine in treatment-resistant depression. Evidence suggests that compared to TCAs, MAOIs may be particularly useful in the treatment of atypical depression. Although efficacious in the treatment of bulimia nervosa and social anxiety disorders comparative evidence is unavailable. MAOIs should not be used for smoking cessation. There are no comparative trials using transdermal selegiline for depression. Rasagiline was found efficacious in the treatment of Parkinson's disease fatigue although comparative evidence is unavailable. Evidence found no increase in mortality with use of MAO-B agents in the treatment of Parkinson's disease. Comparative evidence is lacking for MAO-B therapies in Parkinson's disease, although MAO-B therapy was no more effective than other anti-Parkinson therapies it may be better tolerated.

MAOIs may increase the risk of suicidality in young people and may activate mania/hypomania in patients with undiagnosed bipolar disorder. Due to the risk of serious adverse events these agents are not typically used first-line for depression or Parkinson's disease. Safety issues include potentially fatal serotonin syndrome and hypertensive crisis, as well as cardiotoxicity, postural hypotension, seizure threshold lowering, withdrawal reactions, extended-

severe toxicity in overdose and interactions with other CYP2C19 metabolized medications. Patients must be willing to adhere to dietary tyramine restriction.

MAOIs exert extended effects after drug discontinuation due to their irreversible binding to monoamine enzymes. Regeneration of the enzyme requires up to 14 days. Caution must be exercised when these agents are used in combination with other medications. Of particular concern is the risk for serotonin syndrome. Use of an MAOI and additional medication which increases serotonin levels, especially one that increases serotonin by a different mechanism, may result in serotonin syndrome which may be fatal. Significant reactions may occur with SSRIs and linezolid. The syndrome may occur in a dose-dependent fashion with meperidine, tramadol, methadone, fentanyl and dextromethorphan. Of the TCAs, clomipramine is associated with the greatest risk.

Overall, the MAOIs are not first–line therapy for the treatment of depression as safer alternatives are available, although they may afford a benefit for patients with resistant or atypical depression. Comparative evidence is lacking for the nonselective MAOIs as well as the selective MAO-B inhibitors.

Comparative evidence for the nonspecific and MAOI and specific MAO-B inhibitors is lacking. Available evidence is from older trials in which methodological flaws, heterogeneity and bias are common. The MAOIs are not indicated as first–line therapy for the treatment of depression as safer alternatives are available, although they may afford a benefit for patients with resistant or atypical depression. Available evidence does suggest that phenelzine may be superior to isocarboxazid in inpatient treatment of depression while no difference was found between phenelzine and tranylcypromine in treatment-resistant depression. There are no comparative trials with transdermal selegiline and other MAOIs indicated for depression.

Evidence found no increase in mortality with use of MAO-B agents in the treatment of Parkinson's disease. Comparative evidence is lacking for the MAO-B agents, selegiline and rasagiline. Evidence indicates that MAO-B therapy, while not more effective than other anti-Parkinson therapies, may be better tolerated.

Safe use of MAOI medications incudes consideration of the extended inhibition of MAO activity, drug interactions at hepatic microsomal enzymes, cardiotoxicity, hepatotoxicity, lowering of the seizure threshold, the potential for tyramine-mediated hypertensive crisis and serotonin syndrome.

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