

Appendix 2

SPECIFICS OF INDIVIDUAL DRUGS

General information

Presentation

The list in the first appendix tells the most common name of the antiparkinson's drugs; the individual drugs are presented in this appendix by those most commonly used names.

This appendix has a short (one- or several-page) section for each of the drugs. The material was culled from the various drug inserts, drug manufacturer's advisory web sites, the *Physician's Drug Handbook* (Springhouse, Springhouse PA 2002), and *A Primer of Drug Action* (Robert Julien, MD, PhD, Henry Holt and Company, New York, NY, 2001), as well as from our patients' experiences.

Each section starts with general information about the drug, anecdotal observations from users of the drug, and then shares the official information provided by the manufacturer regarding how the drug is purported to work, the suggested dosing, and the format (tablet or capsule, and amounts) in which the drug is available. Some of the drug sections have short, demonstrative case studies stuck on at the end. Most of the text of this book applies to dopamine-enhancing drugs in general; the drug-specific information is contained in this appendix. There are interesting side notes included in the drug-specific information that may actually be of general interest. If you have the time or inclination, you may want to read about all of the drugs rather than just the one or two that you are taking or considering. By looking at all of the drug methods being used one gets a fuller understanding of the pharmaceutical approaches being used in the western battle against Parkinson's.

The organization of this section is somewhat alphabetical by drug name or group. In the cases of the several agonist and digestion inhibiting drugs, the drugs are grouped together by category.

The listing order is as follows:

Agonists

- Permax
- Bromocriptine
- Mirapex
- Requip
- Cabergoline

Amantadine

Artane

Atenolol

Digestion inhibitors

- Comtan

- Tasmar

Eldepryl

Appendix 2 – Drug details

Mirtazapine
Sinemet (regular and CR)

Drugs not included

People with Parkinson's are often taking other drugs as well, including antidepressants, blood pressure medications, heart drugs, and anti-osteoporosis drugs. Most of these drugs have powerful effects on the body and mind. When combined with antiparkinson's drugs, the effects can be amplified or negated.

Do not expect your doctor to know about all the possible interactions. You will be lucky if he has had the time to study the side effects of the drugs he is giving you, let alone the drugs prescribed by your other doctors. As for the effects of the drugs in combination, most of them are not known unless they are so dangerous that they have caused life-threatening situations. It is likely that moderate problems caused by your drug combinations have never even been reported, or, if reported, they have been lost in the great tide of random information.

Your pharmacist, on the other hand, may be extremely helpful, having more time to work with you and greater depth of information than your doctor. MDs spend a small amount of time learning which drug to use for what ailment. Once they are out of school, they may or may not keep up with the changes. Pharmacists spend almost all their time learning about drugs and must keep up with the new drugs – they are filling orders for them.

If you are taking a drug that is not listed in this section, please find out as much as possible about your drug. Learn how it works. Once you know how it works you might (or might not) be able to anticipate how it might exacerbate or decrease the side effects of your other drugs.

About side effects and overdose information

A partial listing of side effects (adverse effects) of each drug is included in this appendix. Adverse effects should be thoroughly studied by anyone taking that particular drug: they provide a good picture of just what the drug is doing to the body in addition to providing the desired benefit. Please bear in mind that many adverse effects of drugs do not stop after the drug is discontinued; the adverse effect may well become a permanent alteration to one's physiology.

Please study the symptoms of overdose as well. A safe amount for one person may well be an overdose for another. The word "overdose" does *not* mean "took more pills than prescribed." An overdose is what happens to your body if the drug is too strong for *you* or you are taking more than agrees with/is safe for *you*. With this latter meaning we can better interpret a manufacturer's warnings such as "dyskinesia is a symptom of levodopa overdose." The meaning is this: if dyskinesias occur, you are taking too much of the drug, whether or not your doctor prescribed that amount, and whether or not it is the officially recommended dose. If you are having symptoms that correspond to symptoms of overdose, you are in trouble, and you need to work with your doctor to get off the drugs or get your drugs down to a level where the symptoms of overdose are no longer occurring.

Drugs can create unusual or rare side effects that are not listed in the drug inserts or in this book. Everyone will react a little differently to drugs. That's not surprising –

people react differently to mild foods, so it is no wonder that they all react slightly differently to powerful drugs.

Milk is a good example of a food that is presumed safe. Some people cannot digest milk products. Those who cannot digest milk have a variety of symptoms, or side effects, from drinking milk. These adverse effects can include but are not limited to headache, digestive pain, diarrhea, chest pains, asthma, skin rash, and several dozen other reactions. Some of these reactions can be so severe that they require medication or oxygen support. Even so, we do not put warning signs on milk cartons.

In the same way, many drugs can have dangerous or unexpected side effects in individuals. Some patients notice a particular new symptom after taking a drug and refuse to credit their own suspicion that the problem is drug related, simply because the problematic symptom is not included in the list of official adverse effects. Such a patient, finding his symptom is not included in the list of adverse effects, may decide that he is only imagining the problem, or that it is not drug related. This patient may be wrong. If a drug sets in motion a deleterious symptom in an individual, it does not matter one iota if that same symptom does not appear in most other people using the drug.

“If it’s for sale, it must be safe” = not true

Let’s consider a familiar example: most people can eat peanuts; a peanut-sensitive person can die if he eats a single peanut. Even so, peanuts are not sold with warning inserts. Drugs are nowhere near as well-studied and tested as foods. How drugs work is often not understood. Most people want to believe that the mechanisms of these drugs are understood and that drugs must be proven safe in order to be sold. This is not true. In order to be approved by the US Food and Drug administration (FDA), drugs must not kill the small group of healthy young test people during the short period during which the drugs are being tested. Even drugs that are proven to be dangerous may be approved by the FDA if the risks of the drugs are weighed against the benefits and found to be slightly beneficial. Tasmar is an antiparkinson’s drug in this category. It is so dangerous that it is illegal in Canada and the doctor’s instructions suggest that it only be used as a last resort, and the patient should sign a note saying he has been warned. However, on the off chance that this drug will be beneficial when no other drugs help, the patient may choose to take this drug despite the liver damage that it causes. I have had many patients who have been prescribed this drug and their doctor had no idea whatsoever that it was considered a high-risk drug of last resort. So the patient must be the one to study up.

Remember, all drugs carry risks. Even drugs that are dangerous can be approved for use.

So study the side effects, learn the signs of overdose and be familiar with the drug warnings. These warnings exist because drugs, by their very nature, are powerful, body-altering substances. Some drugs can improve some aspects of quality of life. Others can be life-preserving. All of them have risks and side effects. Judicious use of drugs requires balancing the benefits against the necessary damage that they might do.

The drug insert

Although the information in this appendix is as up-to-date as possible in 2003, new information comes up all the time. The manufacturers are required to put the new findings and changes into the drug inserts. Please learn to read the drug insert. At least

Appendix 2 – Drug details

once a year reread the insert on your drugs to see if anything has changed, or if new warnings have been added. Every doctor should review the drug inserts once a year for every drug that he prescribes. I do not know any that actually do. Even though the insert warnings grow and change constantly and established drugs regularly make headlines when they are discovered to have been too unsafe, I know of doctors who state, “I’ve been using this drug on several patients for years now – so it must be safe.” You cannot assume that your doctor has kept up-to-date or that he understands that not all people are alike. After all, a major premise of modern medicine is that people *are* alike. People’s bodies are supposed to work like machines. Differences between machines are flaws according to some doctors, and not manifestations of the individuality of every soul.

Marketing brochures

The glossy sales brochures that accompany some drugs are NOT the drug inserts. The drug insert is usually printed in extremely small letters on a very thin sheet of delicate paper. It may feature a drawing or two of an indecipherable chemical diagram, a chart or two of encoded test results, and is written in technical language. The drug insert is not user-friendly. It looks like something that you are supposed to throw away without reading. In general, if the material given to you by your doctor has photos of smiling people playing the harmonica or enjoying a lemonade with a loved one, that is NOT the drug insert – that is advertising. The sugarcoated advertising version of the drug risks or side effects is what the drug company wants you to know. This reassuring handout may list one or two side effects; it will not tell you the whole story. Even the insert, though going into the test results more deeply, may couch the testing results in the most positive light, even to the point of being misleading.

For example, even if the drug was tested on 1000 people, the drug insert may only show the results of a secondary test that was run on 20 people, in order to minimize the numbers of people with problems. The thinking here is that the patient, and even the doctor, will be less alarmed if the insert says only one person out of 20 died due to the drug than if it stated that 50 out of a thousand died, although the percent is exactly the same.

Unless you note how many people were in the study, you may be deceived into thinking the side effects are less frequent than they really are. It might not occur to you from a casual glance at the statistics on the insert that the study quoted on the insert only reviewed the results of 20 people, all of whom were healthy 20-year-old college students, and not the results of the larger testing that was done prior to final approval. If you read the fine print, however, and see that, although 1000 people were tested, the insert only includes a chart of results based on a group of 20 people, and even in that smallest possible sample, one person died from the drugs, you may be more concerned. So, read the insert, and be smart.

Some companies no longer provide inserts with the drugs – you must ask your pharmacist for a copy of the drug insert information. If you get your drugs by mail, the provider should be able to get you a copy of the drug insert.

Drug insert translations into English

Here are explanations for some terms that might show up on the drug insert:
P.O.: drug is taken by mouth (as opposed to shots, rubbed on the skin, or other method).
b.i.d.: twice a day
t.i.d.: three times a day
q.i.d.: four times a day
q: every
CNS: central nervous system (brain, spinal nerves)
CV: cardiovascular system – pertaining to the heart and blood vessels
EENT: eyes, ears, nose, and throat
GI: gastrointestinal: pertaining to the mouth, stomach, intestines, digestion
GU: kidneys and urinary tract
Hematologic: pertaining to the blood cells
Hepatic: pertaining to liver
Renal: pertaining to kidney
Pulmonary: pertaining to lungs
Contraindication: situations in which this drug should not ever be used.
Interaction: what happens if you combine this particular drug with other drugs or substances.

AGONISTS

PERMAX

Permax is also commonly known as **Pergolide**.

Permax is a dopamine agonist. A dopamine agonist is a dopamine substitute that can imitate dopamine in so far as it stimulates some nerve receptors that ordinarily are only stimulated by dopamine. Permax stimulates D1- and D2-type dopamine receptors. Permax is derived from ergot, a fungus of rye. In the middle ages, the bright eyes and dyskinesias precipitated by eating moldy rye were called St. Vitus's dance, and were considered to be a form of divine ecstasy or witchcraft, depending on one's persuasion.

Permax compared to other agonists

Permax, like all agonists, has many side effects. (Despite the similarities of the agonist side effects, each of the agonists is slightly different and affects individuals differently. Some people do well with one agonist and do not do well with another.) While dyskinesia is recognized as a symptom of dopamine excess, people once thought the ergot from which Permax is derived caused the extreme forms of mental confusion and gastrointestinal pain that can be set in motion by the use of the drug. It was hoped that the new synthetic agonists that contain no ergot would have fewer side effects. However, the newer agonists also have gastrointestinal and hallucination side effects, plus other problems. It may be that the side effects are in fact not caused by the unavoidable ergot proteins but by the dopamine-enhancing properties.

In our experience, the chief difference between the agonists is the type of dopamine receptor that is stimulated. Permax stimulates D1 and D2 dopamine receptors. With Permax, compared to the other agonists, the spine and the low back in particular seem to receive more than their share of the dopamine stimulation.

Permax and back pain

We suspect that D1 and/or D2 receptors may play a role in stimulating the muscles of the low back and abdomen. Several patients have noticed their low back muscles become extremely weak during reduction of Permax and their abdominal pain and spasms decrease. The low back weakness is so extreme that the back may become severely bent, with the head being down between the knees. One patient had to shower by bracing the top of his head against the shower wall and his buttocks against the opposite wall. Another simply walked around with his head facing his knees for several months. This condition can last for more than half a year. Although a few unmedicated PDers have manifested this pattern during recovery, we have seen a disproportionate amount of this severe back weakness in our Permax-reducing patients. It is especially interesting because Mirapex-reducing patients seem to have more problems with their neck muscles becoming limp, so that their heads bob limply on the necks following a reduction. Considering that Permax patients have more back pain and tightness in the back and chest, and Mirapex patients tend to have more problems with severe tension in the neck and low blood pressure (possibly related to the blood pressure-regulating sinus in the neck), it may turn out that the Mirapex-stimulating D2/D3 receptors are directed more to the neck muscles and D1/D2 receptors to the low back and genitals. Of course, both drugs can cause low blood pressure and excess muscle tension, but in general, Permax is

more often associated with back pain and abdominal pain than are the other agonists. Then again, Permax has been out longer, and therefore more side effects have been recognized.

Permax reduction

Permax reduction can cause all the usual symptoms of drug reduction. The drug reduction cycle with Permax is slightly different from the cycle with L-dopa. There is less of a vacation, and the reduction cycle lasts longer, sometimes taking five or six months before there is a noticeable lifting of mood and movement. Also, the long-term yearning for the drug seems to be slightly stronger than with levodopa. This is characteristic of all the agonists.

Although the newer, synthetic agonist drugs take longer to build up in the brain, Permax, derived from a plant, is somewhat fast working. Reductions in Permax are usually noticed within a day or two, and subsequent drug reduction symptoms grow in intensity over a period of months and can last for up to half a year. Long-term, lingering desire for Permax may be permanent. As noted above, Permax reduction can lead to a profound relaxation of the lower back muscles. The subsequent supreme bending of the back is not the same as the hunched posture of Parkinson's disease. The classic PD hunch is tight and rigid, and is primarily driven by the rigid stomach channel muscles of the mammary line pulling down on the shoulders.

The heart valve problem

Currently (2003) at least three law firms on the Internet are hoping to cash in on a guess by the Mayo clinic that Permax may have contributed to heart valve disease in the cases of three women who took Permax daily for three to seven years. These firms are advertising for people who have heart trouble and who took Permax, in hopes of making Permax cough up some money. The law firms will, of course, receive some portion of the cash. These firms may be stymied by the recent finding that people with Parkinson's generally have decreased nerve activity to the heart. This decrease in heart nerves, and not necessarily the Permax, may have contributed to the valve problem, in which case, the law firms will not have a big money case after all. However, it may be that dopamine-enhancing drugs do have a deleterious effect on the heart. Most of them can, after all, cause dyskinesia in the heart (heart arrhythmia), which may have an effect on the health of the heart valves. Much research remains to be done.

Manufacturer's recommendations

The starting dose for Permax is .05 mg/day, for two days. After that, the dose can be increased gradually by .1 to .15 mg/day over the next twelve days. After that, increases of up to .25 can be made every three days until "optimum response occurs." The manufacturer does not state what is meant by "optimum response." The average therapeutic daily dose is 3 mg/day. Neither maximum dose nor advice about drug reduction appears in the *Physician's Drug Handbook*.

Format

The pills are available in .05 mg, .25 mg, and 1 mg doses.

Known side effects

Most side effects of Permax are similar to those created by all dopamine-enhancing drugs. The listed adverse effects include: tremor, twitching, dyskinesia, abnormal gait, muscle tension, dystonia, hallucinations, anxiety, personality disorder, psychosis, depression, confusion, insomnia, breathing irregularity, low blood pressure (even to the point of passing out), abnormal dreams, speech disorder, pounding heart beat (palpitations), sinus problems, double vision, dry mouth, distortion of tastes, abdominal pain, nausea, constipation, diarrhea, anorexia, blood in the urine, urinary tract infections, urinary frequency, anemia, pain in the chest, neck or back, and flu-like symptoms. There are other adverse effects as well.

Please study the insert for this drug, or check the Permax website on the Internet to find the latest listing of adverse effects. You will need to go to the page with “full prescribing instructions” and use the magnifying glass – the warnings for this drug are in impossibly small lettering.

The manufacturer warns that low blood pressure, hallucinations, heart palpitations or arrhythmias, or involuntary movements (dyskinesia) are signs of “toxicity.” This means that these are *not* acceptable side effects; these are danger signs, signs of overdose. In case that one got past your doctor, who may think that dyskinesia is “normal” for Parkinson’s disease, the manufacturer says right out that dyskinesia from Permax indicates toxic levels of the drug.

Ivy

One of our patients, Ivy, had been taking Permax and Eldepryl for several years. Ivy was 53 years old and had been diagnosed with Parkinson’s four years earlier. She was very petite but vigorous, had been very healthy, a hiker and practitioner of yoga. She got off the Eldepryl first, and then very slowly weaned herself from the Permax. Ivy’s reduction rate was as follows: over nine months, she reduced from 3 mg/day to none. Her first reduction was from 3 mg down to 2.25 mg/day. After three months, she was down to 18.5 mg/week. After that, she decreased by .5 mg/week until she was completely off the drugs. During the decreases, she became increasingly prone to confusion and hypersensitive skin. Within a few weeks of her last dose, she had hallucinations, nightmares, and a feeling that spiders and rats were crawling over her skin. Three months after the final pill was taken, she was still deeply confused, did not want to wear clothes, and would yell at her husband to take her clothes off her when she was not wearing any.

She could not sleep more than two hours at a time until four months after taking her final Permax. Anxiety during this time was almost unbearable; her husband was by her side constantly. Four months after her last Permax, she started sleeping slightly better. Periods after waking from sleep or naps were the worst. She was immobile and felt that she was dying from the extraordinary heat that seared her from the inside. Several hours after waking in the morning, following her pre-noon meditation, she was often able to walk along the beach using full strides and could go up and down the stairs easily, but the burning and terrors would start up again during her sleep and following any wake up.

One of her more interesting side effects during drug reduction, one that we had not seen with other drugs, was extremely severe hot flashes and an acidic feeling and a “severe, excruciating, dry stretching” in her vaginal area. Tests for urinary tract infection and sexually transmitted disease came back negative.

Appendix 2 – Drug details

Fourteen months after her last Permax, the excruciating, paralyzing heat events, during which she felt as if she was being burned alive from the inside, and the fear that she would spontaneously combust, and the frantic nightmares that occurred whether awake or asleep had decreased from nearly constant to intermittent. Some days she only had a few hours of the searing pain and debilitating anxiety. Sixteen months later she was able to recognize, with her patient husband's help, that she had less pain on days when she was surrounded by positive people and close friends. After eighteen months she was able to recognize that terror was the underlying emotion during her episodes of immobilizing heat, in which it felt as if her body's normal heat regulating mechanisms went berserk, and overcome the blind fear that saturated her mind every time she had to make a transition from sleep to wakefulness. Despite her awareness of the emotional component and her avoidance of fear triggers, she was still, eighteen months after stopping Permax, very much at the mercy of her drug withdrawal symptoms.

Permax and sex

Curiously, just before she started decreasing her drugs, her husband mentioned that he'd appreciated her medications: they increased her sex drive. We have to wonder if her many years of false sexual stimulation from the drug played a part in creating the agonizing burning and pain in her genitalia after she reduced and then quit Permax. It would seem to make sense. We learned via the Internet that Permax has been discovered by the party-drug, sex-drug crowd. One site on the Internet advertises Permax as a sexual enhancer/libido raiser, and charges \$29.00 per pill (!) for members of the website club. I suspect that this is illegal.

It is probably just a matter of time before all the antiparkinson's drugs are being used for partying and sex-enhancement because of their supreme dopamine-enhancing properties. Consider that the illegal, dangerous drug Ecstasy was first used as a dance-hard party drug and was later found to give a short-term, dose-related decrease in Parkinson's symptoms. Now, in the inevitable switch, the anti-PD drugs are being discovered by the get-stoned-let's-party set. The advantage of Permax is that it is legal if obtained with a prescription, unlike cocaine and methamphetamine, two milder but still popular – but illegal – dopamine-based sex-enhancers. Online drug sellers that provide prescriptions over the Internet by request can mail this perfectly legitimate drug to users.

The Internet site that I found during a search for Permax-for-sex did warn “doses of Permax for sexual enhancement are much lower than those for the treatment of Parkinson's disease.” This same website also featured articles on: “Nature, our enemy” and “Neuropharmacology – the new route to happiness.”

Sex and the low back

In Asian medicine there is a strong connection with the lumbar vertebrae and the energy that is directed to the genitals. Even in western medicine it is now recognized that the nerves to the genitals emerge from the lumbar spine. Considering the influence that Permax seems to exert on the lower back, causing muscle tension and pain especially in the low back, and extreme failure of the back muscles during Permax reduction, it is very possible that the drugs also are producing a surge of energy to the genitals. During drug reduction, the decrease in vitality in the genitals might be the cause of the disordered vaginal nerves/secretions that Ivy has suffered.

It is recognized that bromocriptine, a semisynthetic ergot used as an antiparkinson's dopamine agonist, causes stimulation of the pituitary gland as well as affecting ovarian function and lactation. It can be helpful in restoring menses in some premenopausal women whose menstrual cycles have stopped. This would also point to a relationship between this close cousin of Permax and sexual function.

Ivy, five and a half months later

Five and a half months after taking her last Permax, Ivy started to have moments of less sensitivity in her skin and less confusion. Her children visited her for a week at this time and, though she was drug-free, she felt "On" for the first time since she started her drug reductions. Her mood and movement were perfectly normal, and her sleep was good. She was On the entire week. When they left, she was Off for three days, and then went On again. She may hover between On and Off for years, remaining highly susceptible to changes in mood, weather, and illness.

BROMOCRIPTINE

Bromocriptine is also known as **Parlodel** and **bromocriptine mesylate**.

Bromocriptine is a dopamine agonist. We have only seen three patients taking this drug. Therefore I do not have much to add beyond the material available from the *Physician's Drug Handbook*.

Bromocriptine is a semisynthetic version of the alkaloid derived from ergot, which is the main ingredient of Permax. Most of the information about Permax in the preceding pages also pertains to bromocriptine. The most prominent exception is that bromocriptine does not have warnings about hallucinations.

However, before jumping to any conclusions, Bromocriptine is associated with “mania, delusions, and depression.” It may be simply a choice of words that aligns “hallucinations” with Permax and “delusions” with Bromocriptine.

This drug, like most of the antiparkinson's drugs, may take many weeks, even months, to obtain full effect. It is interesting to note that when this drug is used for hormonal imbalance, it may take up to 24 weeks before the effect is evident.

Our very limited experience with Bromocriptine included one patient who added it to her Sinemet regimen when she started having Offs in the evening. (She had been noticing recovery symptoms for several months before her Sinemet became problematic, building up to powerful shaking by the end of the day.) When she added Bromocriptine to the Sinemet, she started having strong shaking throughout her body about an hour after each dose. The evening dose was the worst – an hour after taking it, the shaking was extremely powerful and would last for nearly two hours. She assumed the Parkinson's had taken a dramatic turn for the worse and was thinking of adding a new drug to the mix until it was pointed out to her that her worst symptoms corresponded to one hour after pill time, and that they might be the result of building up of meds during the day.

Manufacturer's recommendations

This drug should be started at a low dose, 1.25 or 2.5 mg/day, with meals. The dose can be increased by 2.5 mg/day for 14 to 28 days, or until a therapeutic response is attained. The dose should not exceed 100 mg/day.

Format

2.5 mg tablets

5 mg capsules

Known side effects

Side effects are mania, delusions, insomnia, seizures, depression, drowsiness, lightheadedness, low blood pressure, nervousness, stroke, acute heart attack, blurred vision, nausea, abdominal cramps, constipation, diarrhea, and urinary retention. We have seen amplification of tremor occur after starting Bromocriptine; however, this is not an officially noted adverse effect.

Warnings

Do not use with alcohol: alertness and coordination may be impaired.

MIRAPEX

Mirapex is also known as **Pramipexole hydrochloride**.

Mirapex is a synthetic dopamine agonist. The researchers had hoped that by building an agonist molecule in the lab, rather than deriving it from ergot, they would be able to sidestep the gastrointestinal and hallucination problems of Permax. However, those problems remain and would appear to be a part of agonist action in general. Strangely enough, Mirapex actually has a few powerful side effects that, for some people, are worse than the problems of Permax. The most problematic of these is narcolepsy (sudden, randomly timed episodes of going from wide awake to deeply asleep, even while engaged in physical and/or mental activity). Many instances of suddenly falling asleep while under the influence of Mirapex were recorded in the first few years after Mirapex was approved. In my own small practice, I've had three patients who have abruptly fallen asleep at inappropriate times, including while driving. One patient fell asleep three times in one week, each time while driving. After stopping the Mirapex, the narcoleptic attacks ceased.

Insomnia, narcolepsy, and turkey dinners

Mirapex and Requip, another agonist, can cause *both* insomnia and narcolepsy, sometimes on the same day, a mere six hours apart. This effect may be due to the agonist's excess stimulation of the stomach. A Thanksgiving dinner example shows how this seeming conflict between insomnia and narcolepsy is actually a normal response to excess stomach stimulation. Many people fall into a stupor after an overlarge meal such as Thanksgiving dinner. The heavy stimulation of the stomach dulls the mind and lowers the eyelids. A short, inadvertent nap following such a meal may be the rude but unavoidable result of overindulgence. However, that night, due to excess food remaining in the stomach, sleep may be poor, with much tossing and turning, if not outright discomfort. Excess stimulation of the stomach causes both conditions: drowsiness and abrupt nodding off, *and* inability to fall into a deep, restful sleep.

The other aspect of excess stomach stimulation, which is intestinal discomfort, can also be a side effect of Mirapex and Requip.

Low blood pressure

Mirapex often causes problems with hypotension, also known as low blood pressure. Orthostatic hypotension (getting briefly dizzy when standing up after having been sitting or lying down, sometimes called a "head rush") is also a problem. Even though PDers tend to have low blood pressure as a side effect of the PD, Mirapex can exacerbate the problem. I have had several patients who tried Mirapex briefly and then stopped, due to the head rush problem. One patient, defying the instructions, started Mirapex with a high dose ("It's such a tiny pill, it can't really do anything. I take L-dopa, and that's a much larger pill...") and fainted twice due to such dizziness. It is to a large extent due to this "head rush" symptom that people must build up slowly to a therapeutic level with this drug. Then again, as noted earlier, my patients who have increased far more slowly than suggested by the manufacturers, spending two to three months at each

dosage level instead of two or three weeks, have found that they get a nice result from the medication at a fraction of the suggested dose – it just takes time.

Neck tension

Mirapex seems to cause an increase in tension in the muscles along the front-sides of the neck (anterior face of the sternocleidomastoids). This tension may contribute to the head rush. A major component of the blood pressure monitoring system (the carotid sinus) is located right under these muscles. It may be that either a direct effect on the muscles of the sinus or an effect on the muscles that lie atop the sinus creates tension and pressure on the sinus, yielding a false signal of excess blood pressure.

The body's appropriate response to an increase in pressure in this area is to dilate the blood vessels and relax the heart rate in an attempt to reduce blood pressure. This purposeful lowering of the blood pressure is possibly a response to a phony "high pressure" alert caused by Mirapex-related muscle tension. The drop in blood pressure then leads to a head rush, and even passing out, when changing from a sitting position to a standing one.

Neck muscles

Patients who have taken Mirapex for a long time find that the neck muscles can be extremely wobbly after stopping the Mirapex. Though this drug is fairly new, I was fortunate to have a patient who had taken Mirapex for six years when I met her in 1999 – she had been in one of the studies that tested Mirapex prior to its approval. When she slowly weaned herself off the Mirapex, her head wobbled so loosely on her neck that she actually stacked her law books up on her desk at work and propped her chin on the top book; she could not support her head any other way. At home she had to stay lying down or support her head with her hands for many weeks after finally getting off Mirapex. Mirapex's extreme tightening of the front-sides of the neck, exaggerating the forward thrust of the neck seen in Parkinson's, coupled with the collapse of the neck when the drug is withdrawn, suggest that the D2 and D3 receptors stimulated by this agonist play some part in the regulation of the upper spine/neck muscles. This neck effect of Mirapex contrasts with Permax, which as you will recall does the same thing but in a different area, the lower back. Both cause excess tension or, upon reduction, collapse.

Stroke

The first four Mirapex patients that I worked with all decreased their Mirapex very quickly (over a period of two weeks or less). They all experienced symptoms of slight stroke (broken blood vessel in the brain). These symptoms included sudden loss of use of one limb (not necessarily on the Parkinson's side), suddenly impeded speech, personality change, and other symptoms of mild stroke, although none of them had a brain scan done and all of them recovered from their symptoms within a few weeks. These events were preceded by a feeling of excess pressure in the head, heat in the head, or a feeling as if something was going to explode. In the drug literature for Mirapex, there are warnings about over fast reduction causing neuroleptic malignant syndrome (elevated temperature, muscular rigidity, altered consciousness, and blood pressure changes). This syndrome is attributed to something going haywire in the autopilot portion of the brain.

It does seem as if the blood pressure pendulum can swing from a drug-induced Too Low all the way over to Too High when the drug is withdrawn. The good news is the manufacturers of this drug now recommend that this drug be reduced slowly. The bad news is they advise “one week” as being appropriately slow.

My subsequent patients did much better: they reduced over a period of months, not seven days. They all went their own ways, but in general they cut back by about .25 mg per reduction, and then they waited several weeks, minimum, before making another reduction. When they got down to .125 mg three times a day, they reduced by eliminating one dose of the three – taking only two doses per day for several weeks. After stabilizing at this level, they reduced to one dose per day for several weeks, and finally went down to none. Though some doctors scoffed, insisting that these low doses were doing nothing, I saw no more of the stroke-like symptoms after my patients started doing the slow decrease method.

Happy hallucinations

Most of the antiparkinson’s drugs can cause hallucinations. Some notoriously cause terrible visions and nightmares. Mirapex visions are refreshingly harmless, even endearing. Most people enjoy, rather than resent, the playful creatures and little smiling children that appear under the influence of Mirapex.

Long-term depression after Mirapex reduction

The happy hallucinations and spirit-lifting effects of Mirapex have, of course, a backlash: when this drug is stopped, the vague sense of depression, irritability, and/or hopelessness can last for more than a year after the last crumb of Mirapex is taken.

Combined with Sinemet

I have seen many patients whose MDs have mistakenly told them that the agonist must be taken at the same time as the levodopa to have any effect. Some doctors actually have their patients taking this drug six or more times a day, simply because the patient is taking levodopa that many times a day. These doctors are confused and wrong. Mirapex is supposed to be dosed three times a day. Mirapex is a slow-working drug. Unlike levodopa, it does not wear off in six hours, or even twelve. My patients who only take agonists have never noticed a distinct On/Off from the drugs, and their improved mobility does not appear to be dose related whatsoever. They do not notice any difference if they forget a pill now and then.

The antiparkinson’s effect of Mirapex and Requip seems to be a slow, cumulative effect, not a quick response. It is probably due to the unpleasant side effects that this drug can have on the gastrointestinal tract, including narcolepsy, that this drug is recommended to be taken three times a day rather than all at once.

However, our patients who have recovered and continued to take Mirapex (such as Becky and Rudyard) have found that Mirapex has, for them, a quick onset and wearing-off time. The effect may be felt within an hour and wears off within three hours. This is very different from our unrecovered PDers who took Mirapex; for them, the antiparkinson’s effect was slow on and slow off, although the stomach (gastrointestinal) symptoms such as stomach discomfort and narcolepsy were still fast acting.

Appendix 2 – Drug details

Manufacturer's recommendations

Start by taking .125 mg three times a day. Every week or so increase each of the three daily doses by .25 mg until the therapeutic level, 1.5 to 4.5 mg/day, is reached. Stay at this maintenance level, and continue to take the pills three times a day.

Format

To accommodate the slow dose escalation, this drug is available in many dosages. Many doctors prescribe the starter kit, complete with all the various dosages and a calendar for tracking drug increases, for patients beginning Mirapex.

Mirapex is available in the following doses:

.125 mg (an eighth of a milligram)

.25 mg

.5 mg

1 mg

1.5 mg.

Known side effects

Known side effects for Mirapex are dyskinesia, twitching, muscle spasm, dystonia, gait abnormalities, tremor, dizziness, low blood pressure, sleepiness, narcolepsy, insomnia, sleep disorders, hallucinations, confusion, thought abnormalities, paranoia, delusions, chest pain, edema (water swelling), double vision, vision abnormalities, dry mouth, sinus problems, anorexia, nausea, constipation, difficulty swallowing, arthritis, muscle heaviness, and dyspnea (breathing problems).

Precaution

Dosing may need adjusting in patients with kidney problems.

Levodopa dosage may need to be reduced.

REQUIP

Requip is also known as **Ropinirole hydrochloride**.

Requip is a dopamine agonist that is known to stimulate D2 receptors. It has much in common with Mirapex, including the problems with narcolepsy, passing out from low blood pressure, and gastrointestinal disturbances.

We have not seen enough patients in our clinic taking or reducing Requip to make generalized statements about this drug, although we have seen people who have the problems listed above even in our limited experience with this drug.

Adverse effects

In general, the information, warnings, interactions and contraindications for Mirapex in the section preceding also apply to Requip. The main difference between the two, as far as what we have seen in clinic, is that the dosings and pill sizes are different. The absorption rate is similar for the two, the half-life in the blood is longer for Mirapex (8 hours, as opposed to 6 for Requip), but, overall, the two drugs are very similar.

Manufacturer's recommendations

Starter dose is .25 mg, three times a day. Increases in dose are made weekly, increasing each dose by .25 mg for the first few weeks. After week four, the dosage can be increased by 1.5 mg/day (.5 mg per dose, three times a day) until a dosage of 9 mg/day is obtained. After that, it can be increased by 3 mg/day until the therapeutic level is attained. Maximum dose is 24 mg/day.

Warnings

Like Mirapex, the drug must be reduced slowly or it might produce neuroleptic malignant syndrome (see the section on Mirapex).

As with Mirapex, reduction of levodopa may be needed when Requip is added to the mix.

Mitch

Simply because we haven't mentioned Requip very much in this book, I will include a quick sketch of Mitch. He was taking Requip and starting to exhibit symptoms of recovery. He passed out one morning, about an hour after taking his Requip. His wife found him on the bathroom floor with blood streaming from his nose and from the gash above his eye where he crashed into the toilet on his way down. He had been having dizzy spells and losing his balance for several weeks and had told me that the dizzy spells were getting worse. The second time he passed out he gave me a call. I went over the details of his episodes of syncope (doctor language for fainting – what ladies do, or passing out – what men do). It seemed that his passing out and dizziness were directly related to the timing of his Requip dose: the trouble always occurred about one hour after taking his pills. He reduced his Requip over the course of a month, and the dizziness stopped.

Appendix 2 – Drug details

Mitch is a top neurologist, a professor of neurology at a prestigious medical school. It had never occurred to him to track the timing of the side effects compared to the timing of the dosing. He considered reducing his meds even further but was terrified that he might become depressed, and he chose not to reduce his drugs even though he knew he was becoming overmedicated. He hasn't come into the office since his decision not to further reduce his drugs. Mitch is a highly respected neurologist: he confided in me, "We neurologists don't know what we're talking about when it comes to Parkinson's; we're just making things up."

When I asked him if he would tell his fellow neurologists about his experiences with our Asian medicine program he replied, "No. They would think I was crazy if I told them."

CABERGOLINE

Cabergoline is a European agonist drug. We had only one patient who was using this drug. According to the description, it is a slow working agonist. From what we can figure, it is very like Mirapex/Requip. For information about side effects and mechanism, consider using the Mirapex/Requip information.

AMANTADINE

Amantadine is also known as **Amatadine hydrochloride** and **Symmetrel**.

Amantadine is one of the non-dopamine drugs used for Parkinson's. It is a synthetic form of an amine – a very large molecule family that includes the famous vitamins. Amantadine was first used as an antiviral drug when it was noticed that it seemed to inhibit type A influenza (although the mechanism remains unknown). When used within 48 hours of onset of illness from type A flu virus, it can reduce the duration of fever and other flu-related symptoms. It is usually taken only briefly, the drug being stopped within 48 hours after the illness has passed. Amantadine is sometimes used as preventive medicine; when an elderly person or person with a compromised immune system is exposed to type A influenza virus, he may be prescribed Amantadine and told to take it for ten days following the date of exposure. When used in this protective (prophylactic) manner, the drug may be taken for up to 90 days.

By chance it was noticed that PDeers who took the drug for viral protection appeared to have improvement in their Parkinson's symptoms. The mechanism for this benefit is utterly unknown. Of course, given the current fashion of Parkinson's disease being attributed solely to dopamine shortage, it was guessed that Amantadine might somehow cause a release of dopamine. Based on our observances of PDeers who use Amantadine, and especially those who have tried to stop taking it, we suspect that the helpful mechanism may have to do more with adrenaline than with dopamine.

Our hypothesis has to do with the fact that adrenaline does act as an antiviral, antibacterial agent; when a person is under stress or maintaining a sense of urgency, he is unlikely to become sick. The common scenario in which a very busy person finally gets an overdue vacation and immediately comes down with a bug may be due to the relationships between adrenaline (a.k.a. epinephrine) and norepinephrine (a known immune system booster). In times of intensity of activity and responsibility, a person simply cannot allow himself to get sick. When the pressure is off and the adrenaline drops back to normal, a dormant flu is able to spring forth.

To the above observation we add that Amantadine, unlike all the dopamine-enhancing drugs, does not create mood-enhanced movement or a change in personality. People who take Amantadine notice that they feel like their old familiar, stressed-but-active, pre-PDeer selves again, almost as if the lagging adrenaline had been turned back on.

Also, when Amantadine is decreased, the patient acts as if “the plug has been pulled.” Instead of the emotional jag, insomnia, or shaking that occurs from a levodopa reduction, a reduction in Amantadine usually causes a simple shutdown of motor function, as if the driving force, as opposed to the emotional impetus, has disappeared. In cases of abrupt cessation of Amantadine, the patient may be utterly immobilized, even if he is still taking a full complement of other antiparkinson's medications. One patient, four days after stopping Amantadine cold turkey, described himself as being “frozen stiff, like the Tin Man in *The Wizard of Oz*, before Dorothy brought him the oil can.”

Another peculiar difference between Amantadine and the dopamine-enhancing drugs is that the full effect of Amantadine or Amantadine reduction is usually felt within four days. On the first day of reduction there is usually a slight decrease in vitality. This decrease worsens quickly, and by the fourth day, most of the patients in our experience find that they are completely without motivation or power. Typically, they resume the

drug within five to ten days after reducing it. In our experience of those using Amantadine, only 4 people have been able to stop taking it, though all have tried. Even patients who have been able to decrease Sinemet or agonist drugs have been stymied when trying to decrease Amantadine.

For the above reasons – the creation of viral resistance, and a response to decrease that is both non-emotional and very quick – we suspect that dopamine is not particularly influenced by Amantadine. Instead, I propose that this drug is affecting adrenaline or possibly norepinephrine levels.

Accommodation

Although Amantadine is not addictive in the usual sense, the body can accommodate to it. Within about three months after starting Amantadine, the body compensates by reducing its native adrenaline production (or production of whichever neurotransmitter it actually is that is enhanced by the drug) so that the person is right back where he started: the combined amounts of the drug plus the reduced native amount equals the amount of adrenaline that the body had to begin with. At this point, due to the compensating reduction of native adrenaline, it appears as if the Amantadine is no longer effective, and the PDer usually goes back to his neurologist for something “stronger.”¹

Why mild?

The problem with this drug is, once a person has started taking it, it is extremely difficult to stop. Although this is considered a very mild drug by many neurologists, we have never been able to figure out why. Possibly it is because this drug does not cause dyskinesia. I disagree with this “mild” label: this drug has many side effects (it can be especially disruptive to sleep, causing vivid dreaming and insomnia), it is nearly impossible to stop taking it once a person has started it, and the brain responds quickly to counter the drug, so that the benefit only lasts three months, but the side effects never ease up, and in fact, may worsen over time. Those three months of movement come at a high price: a lifetime need for Amantadine after it no longer provides any benefit.

Manufacturer’s recommendations

PDers may take up to 200 mg/day. If a person is already taking other antiparkinson’s drugs, Amantadine should be started at only 100 mg/day for the first week, and then increased depending on the patient’s response. Although patients may have benefit from doses as high as 400 mg/day, patients should be carefully monitored for any dose higher than 200 mg/day.

Anyone with kidney disease or hemodialysis should let their doctor know that this drug must be carefully monitored, such patients receiving only 200 mg per week, not per day.

This drug must be used cautiously in anyone with a history of seizure, heart failure, liver or kidney weakness or disease, mental illness, light-headedness when standing up, cardiovascular disease, edema (water swelling) in the ankles, and in elderly patients. The manufacturer does not state what it means by “elderly.”

¹ The three month figure is further supported by the manufacturer’s note that this drug does not appear to be effective in its antiviral protection capacity beyond three months. Evidently it takes the body about three months to accommodate to this drug, whether it is used for PD or for viral protection.

Appendix 2 – Drug details

This drug may impair mental alertness.

Parkinson's patients using this drug are cautioned not to stop this drug abruptly, as this might "precipitate a parkinsonian crisis."¹

Format

Amantadine is available in 100 mg tablets, 100 mg capsules, and as a syrup (for dosing small children with immune system weakness). All patients in our experience take the gel capsules. None have been able to find the drug in the tablet form. Patients wanting to decrease this drug slowly have been frustrated by the difficulty in reducing by a fraction of the gel cap. Several patients have written to me stating that they have bitten a hole in the gel cap and squeezed out several drops of the drug so that they can reduce this drug slowly, since slow reduction is recommended by the manufacturer. The few patients who have tried switching to the liquid form of the drug to facilitate drug reduction have had difficulty in making the transition; they have all said that the drug behaves differently or doesn't work as well in the liquid form.

Known side effects

Irritability, insomnia, dizziness, light-headedness, nausea, hallucinations, headache, and vivid dreams are the most common side effects. Other side effects, ones that may be related to the brain's compensating mechanisms (a reduction in zip to compensate for the over stimulation of the drug) are, logically, just the opposite of what you might expect from a stimulant: depression, fatigue, confusion, anxiety, constipation, lack of appetite, vomiting, and dry mouth.

Symptoms of overdose

Tremor, nausea, vomiting, anorexia, seizures, heart fibrillations, slurred speech, blurry vision, urine retention, depression, and the movement extremes of agitation or slowness may all indicate overdose. After reviewing the potentially dangerous side effects, and especially the effects of overdose, and bearing in mind that, once accustomed to the drug, one must continue taking it even after the effect wears off, you may wonder, as we do, why this drug is considered to be a mild, starter drug for Parkinson's disease.

Warnings of risk from combination

Artane: may cause an amplification of side effects, especially confusion and hallucinations, if used with Amantadine. With regard to combining Amantadine and Artane, the manufacturers warn, "Use together cautiously." This euphemism means don't use these two together if you can help it. Jimsonweed, an herbal anticholinergic, in combination with Amantadine, can affect the heart/blood supply system. This combination is to be avoided.

Levodopa: Amantadine may cause increased stimulation to the central nervous system if used with stimulants. Curiously, the manufacturer does not name specific stimulants. Bear in mind that no drug manufacturer wants to write down in cold print that his drug should not be used with other specific drugs; this might lead to decreased sales. Without the word "levodopa" serving as a red flag, the Amantadine warning against

¹ *Physician's Drug Handbook*, Springfield, 2002, p. 31.
512

using in conjunction with “central nervous system stimulants” is more likely to be invisible. Levodopa is a central nervous system stimulant. With regard to central nervous system stimulants, the Amantadine manufacturer recommends, “Use together cautiously.”

Alcohol: Amantadine in combination with alcohol can cause fainting, low blood pressure (dizziness when standing up), confusion, and light-headedness.

ARTANE

Artane is also known as **Trihexyphenidyl hydrochloride**, **Apo-Trihex**, **Artane Sequels**, **Trihexane**, **Trihexy-3** and **Trihexy-5**.

Artane is an anticholinergic: an acetylcholine-suppressing drug. Artane was one of the first drugs used in treating Parkinson's. Back in the days before dopamine was discovered, someone opined that Parkinson's was caused by too much muscle tension. When it was discovered that acetylcholine was the neurotransmitter that triggered muscle tension, it seemed reasonable that an anti-acetylcholine drug could cure the presumed "excess muscle tone" of Parkinson's. Although this theory is now discounted, the sedative powers of anticholinergics do benefit a PDer in this regard: by making the PDer mentally, as well as physically, drowsy and weak, anticholinergics may lull the anxiety-driven tremor and restlessness. The downside is that heaviness of the limbs, a common problem in Parkinson's, is increased by the anticholinergic drugs. Some doctors are now considering that acetylcholine *increasers*, rather than *decreasers*, may be helpful for PDers. Of course, while these drugs may increase muscle tone and vigor, they may also serve to increase the tremor and restlessness.

Side effects following a decrease

Although acetylcholine is not considered one of the addiction neurotransmitters, acetylcholine is one of the neurotransmitters that slowly increase or decrease according to need. Since the drug decreases the amount of acetylcholine present, the brain slowly increases production accordingly. Eventually, the brain can *increase* acetylcholine enough to compensate for the presence of the drug. When this happens, the drug appears to lose its effect.

If this drug is decreased after having been used for more than a few weeks, the compensating increase in acetylcholine will become apparent – side effects that are the opposite of drowsiness and weakness may manifest for several weeks while the brain slowly adjusts the acetylcholine back down. During this time there may be a severe increase in anxiety, insomnia, and nervousness. If tremor is present, the anxiety may exacerbate the tremoring. I have seen intense panic attacks occur in response to a decrease in this drug. The panic attacks ebbed within a month of discontinuing Artane.

Two of our pioneers took Artane (a suppressant) with Sinemet (a stimulant) and had to figure out which drug to reduce when. They both independently came upon the same formula; if the patient slumped weakly in the chair all day, staring vacantly into space, the Artane was decreased. When dyskinesia was foremost, the Sinemet was reduced. Sometimes they would both be reduced at the same time, balancing each other's withdrawal effects.

The manufacturer's recommendations

The recommended dose for *postencephalitic* or *drug-induced* parkinsonism is 5 to 15 mg/day.

Advice from the manufacturer that I have never seen observed by physicians is this: patients with idiopathic Parkinson's (the common type) who use levodopa should take less than the above amount: a mere 3 to 6 mg/day of Artane may be needed if levodopa is also being used.

Older patients (the manufacturers do not specify what they mean by “geriatric”) should use lower dosages. The manufacturer does not state what the lowered doses should be.

Artane should be started off slowly, taking only 1 mg on the first day, 2 on the second, and then increases made of 2 mg/day until the desired dose is attained. The pills should be taken at mealtimes. The sustained release pills should be taken once a day, after breakfast.

Users of this drug should not drive or engage in activities that require alertness until the effects of the drug on the individual have been determined.

Format

Artane is available in 2 mg and 5 mg tablets and in 5 mg sustained release capsules.

Known side effects

The side effects of Artane are just what you would expect from a drug that inhibits the neurotransmitter of strength: weakness and drowsiness. Specifically, the research lists weakness, drowsiness, blurred vision, pressure inside the eyes, headache, dizziness, hallucinations, nervousness, dry mouth, nausea, constipation, vomiting, urinary hesitancy or urinary retention.

Some other side effects may be the result of the body’s trying to balance things out: nervousness and increased heart rate are also recognized side effects. It may be that, in response to drug-induced weariness, the body increases the heart rate in an attempt to overcome the drug. Likewise with nervousness: the drug sedates anxiety in the short term, but when the brain compensates for the drug by increasing acetylcholine to a higher level than normal, the increased NT may cause anxiety and nervousness. Nervousness and restlessness may also increase due to the panic that can set in when the brain feels as if “something is wrong,” a feeling that can be triggered by this powerful muscle sedative.

Recognized symptoms of overdose

As should be expected from a drug that sedates the body and mind, overdose can cause mental symptoms of disorientation, confusion, delusions, anxiety, and restlessness. Physical symptoms can include blurred vision, dilated pupils, difficulty in swallowing, decrease in bowel function or urine release, high blood pressure, racing heart beat, and rapid breathing.

ATENOLOL

Atenolol is also known as Tenormin.

Atenolol is a beta blocker, a type of heart medicine. It prevents the heart rate from speeding up and also reduces blood pressure.

This drug is not a traditional antiparkinson's medication. However, some doctors, recognizing its sedative abilities, have prescribed it to help sedate the anxiety-driven tremor of Parkinson's. Unlike the antihistamines that sedate via drowsiness, a beta blocker sedates by holding the heart rate to a lowered pace. This lowered heart rate in turn reduces one's ability to feel anxiety or excitement. By reducing emotions, this pill can sometimes reduce tremor.

Low blood pressure

The blood pressure reducing properties of Atenolol can be a concern for PDers: many people with Parkinson's have orthostatic hypotension (light-headedness when shifting to a standing position), low blood pressure, or are already taking blood pressure medications. Also, many of the traditional antiparkinson's medications can cause lowered blood pressure. If your doctor prescribes this drug as a way of sedating tremor, stay aware of the low blood pressure side effects.

Other side effects

Other side effects of this drug can include fatigue, lethargy, drowsiness, dizziness, dangerously slowed heart rate, heart failure, high or low blood sugar, nausea, diarrhea, dyspnea (breathing difficulties) and bronchospasm (spasm in the air pipe).

DIGESTION INHIBITORS: COMTAN AND TASMAR

Comtan and Tasmar use different mechanisms to obtain the same type of result. They both block enzymes which otherwise would contribute to the breakdown of levodopa and dopamine in the blood, before the levodopa gets through the blood-brain barrier.

Ordinarily, the body does not want excess levels of blood dopamine floating around and takes great pains to quickly get rid of any excess dopamine by using specific enzymes (COMTs, short for catechol O-methyltransferase). These two drugs prevent these enzymes from doing their job, thus allowing blood dopamine levels to build up to unnaturally high levels. The hope is that more dopamine will make it into the brain if the enzymes are unable to do their job and break down the levodopa or dopamine.

Dopamine digestion, not food digestion

I refer to them as digestion inhibitors, but they do not inhibit digestion in general – they only inhibit the breakdown of dopamine and those foods or chemicals that are similar in structure to dopamine. The idea here is that by inhibiting the enzymes (COMTs) that are supposed to regulate blood (serum) levels of dopamine, the blood can achieve super-high dopamine levels. Then, as this dopamine-rich blood cruises past the brain, the extra dopamine can get sucked inside the blood-brain barrier and help make up the presumed dopamine deficiency in the brain.

These drugs are typically added to the drug regimen when the brain has already started rebelling against the excessive levels of dopamine being shoveled in by other antiparkinson's drugs. Signs of this rebellion range from dyskinesia to freezing and include all the other side effects of excess dopamine. The assumption on the part of the drug industry appears to be as follows: when the brain starts rebelling against excess dopamine, what it needs is even more dopamine. Therefore, these digestion-inhibiting drugs are added to Sinemet to force even more dopamine into an already reluctant and resisting brain.

Increased adverse effects of levodopa

After you finish reading about the digestion inhibiting drugs, you may realize that no one in his right mind will use them – they simply increase the side effects of levodopa. The main reason most doctors do not want to increase levodopa indefinitely is that the side effects become too severe. Doctors who have not read about the mechanism for these digestion-inhibiting drugs think that they are a way to increase dopamine in the brain without increasing the levodopa dose. However, the way that these drugs work is to increase the *effective* amount of levodopa, whether or not the actual dosage of levodopa has been increased. The very effect that the doctors are trying to avoid – too much levodopa – is exactly what happens when taking these drugs. Not one of my patients who have taken the digestion-inhibiting drugs has been able to continue them for any significant length of time – their levodopa side effects became intolerable. Combining the levodopa side effects with the side effects of these digestion-inhibiting drugs makes for a very unpleasant experience. Comtan tends to cause more gastrointestinal problems, stomach pain, and permanent diarrhea. Tasmar causes more liver damage and fatal liver

failure. Neither one is the answer to the question of how to get more effectiveness from one's dopamine without also getting more adverse effects.

COMTAN

Comtan inhibits (blocks) an enzyme (COMT) that is supposed to break down catecholamines. Catecholamines are a member of the amine family. (Amines are a specific type of protein, as noted in the section above on Amantadine.) Familiar (discussed earlier in the text) members of the catecholamine branch of the amine family are epinephrine (adrenaline), norepinephrine (a frontal lobe mood regulator), and dopamine. Ordinarily, the body wants to break down the bloodstream levels of these chemicals very quickly: they are mood and movement regulators whose levels need to change quickly in response to life activities. Comtan prevents the breakdown of these and other catecholamines.

Some medications are also broken down by the anti-catecholamine enzymes. Using Comtan will prevent these medications from being broken down, and the medications may build up to dangerous levels. Therefore, a person using central nervous system depressants, some asthma drugs, the non-selective MAO inhibitors (which may include the antiparkinson's drug Eldepryl, as this drug becomes non-selective if taken at doses higher than 10 mg/day – an approximate number, and all people are different), and other drugs listed on the Comtan drug insert may not be a suitable candidate for Comtan.

Manufacturer's recommendations

This drug is only effective when used simultaneously with a levodopa product such as Sinemet or Madopar (as it is known in Europe). This drug has no dopamine-enhancing properties when used by itself. Therefore, this drug is supposed to be taken at the same time as the levodopa drug is administered. Also, adverse effects such as hallucination, dyskinesia, and other problems of dopamine excess are due to the levodopa drug and not to the Comtan, per se.

Dosage

200 mg taken with each dose of levodopa, but no more than eight doses per day.

Format

200 mg tablets

Adverse effects

Adverse effects of Comtan can include dyskinesia, extreme excess of movement, extreme absence of movement (slowness, freezing), dizziness, anxiety, agitation, fatigue, extreme sleepiness, extreme weakness (asthenia), hallucinations, nausea, diarrhea, abdominal pain, constipation, vomiting, dry mouth, indigestion, taste perversion, bruising on the skin, back pain, dyspnea (breathing irregularities), and sweating.

Warnings

Levodopa dosage should be lowered to avoid adverse effects.

This drug may cause or worsen side effects of levodopa, including dyskinesia or hallucinations, *even if the levodopa dose is decreased* (italics are mine).

Diarrhea usually begins within 4 to 12 weeks after starting Comtan, but it may begin as soon as the first week or not start until after many months of treatment.

Rapid decrease of this drug can cause the same sort of problems as rapid decrease of levodopa (please read chapters 3 through 24), including neuroleptic malignant syndrome.

Keep an eye on blood pressure, be cautious when shifting from a sitting to a standing position, don't drive until you know how this drug will affect your reflexes and alertness, and avoid alcohol.

TASMAR

Tasmar works along the same lines as Comtan, but with this difference: the enzyme inhibited is one also that breaks down red blood cells. It turns out that by inhibiting the breakdown of red blood cells, the rate of levodopa breakdown is also inhibited. The reason remains unclear.

Liver failure

Canada has banned the use of this highly dangerous drug. Logically, no one should use this drug. Even the manufacturers state that “because of the risk of potentially fatal, acute fulminant [rapid, full blown] liver failure, use drug only in patients on levodopa-carbidopa therapy who don’t respond to or who aren’t suitable for other adjunctive therapy.” In common English, this drug should be used only when no other drug is useful, and even then, the user is risking rapid liver failure. The doctor is supposed to discuss the dangers with any potential patient and the patient must give a signed consent form.

Despite this warning, which is one of the strongest ones in the antiparkinson’s armory, this drug is blithely prescribed by some doctors because it is included in the antiparkinson’s list.

Within a month after this drug was approved as safe by the FDA and released to the public with great fanfare, heralded as the drug to use when levodopa was no longer effective, three patients died of acute liver failure. Rather than taking the drug off the market, the manufacturers continued to offer it with this warning: patients using this drug should have a complete liver panel (blood work lab tests) done every two weeks for as long as they are using the drug or at least the first year. After the first year, if the patient is still alive, the liver panel may be done every eight weeks.

Considering how dangerous this drug is, I am not even going to list the manufacturer’s suggestions for usage or the recommended dosage. If your neurologist has told you to take this drug, consider getting a new doctor. If you can’t change doctors, please show your doctor the drug insert and gently inform him that even the manufacturer of this drug presents it only as a drug of last resort and suggests “written informed consent” from the patient.

Adverse effects

The adverse effects are the same as Comtan, with these additional known effects: tremor, excessive dreaming, headache, falling, fainting, loss of balance, speech disorder, chest pain, chest discomfort, palpitation, low blood pressure, ear ringing, swollen throat, anorexia, urinary tract infection, urinary incontinence, impotence, muscle cramps, stiffness, arthritis, neck pain, bronchitis, and upper respiratory tract infections, to say nothing of the fatal liver failures.

ELDEPRYL

Eldepryl is also known as **Selegiline hydrochloride, L-Deprenyl hydrochloride, Atapryl, Carbex, and Selpak.**

Eldepryl is a powerful mood enhancer. One newly diagnosed PD patient started Eldepryl therapy and within a few weeks announced, “If this is normal, then I’ve been depressed my whole life and I never knew it.”

I can often detect if a patient has been taking Eldepryl for more than a few months, in this way: a tremulous vocal quality often develops, as if the user is always on the verge of tears. This vocal trait goes away after the medication is stopped.

Manufacturer’s information

Eldepryl “probably”¹ enhances brain dopamine by blocking the enzyme (MAO²) that normally breaks down certain chemicals, including brain dopamine. At low doses it is thought that this drug selectively (only) blocks the type of MAOs that work in the brain (type B). However, there is reason to believe that it also affects the MAOs that work on stomach chemicals. The manufacturer notes that, since stomach side effects worsen as the dose increases, possibly this drug only affects type B MAOs in low doses and affects other MAOs in high doses. This specious logic is a nice attempt to avoid the larger issue, which is that no one actually knows why this drug helps people with Parkinson’s. It is also a way to avoid being classified as a non-specific MAO inhibitor, a classification to be avoided, because certain other drugs are specifically contraindicated for use with non-specific MAO inhibitors.

Going off on a completely different tack, the manufacturer also volunteers that maybe this drug works by decreasing dopamine reuptake, similar to the cocaine-type mechanism.

Finally, although much attention is drawn to the MAO theory, it is mentioned in the drug books, almost as a shy afterthought, that one reason this drug may help people with Parkinson’s is that it breaks down in the body into methamphetamine and amphetamine. Because meth is a well-known, highly illegal drug, one with many negative connotations (addiction, crime, etc.), it is understandable that the manufacturers might want to play down this fact about Eldepryl. However, even they admit that Eldepryl “has pharmacologically active [understatement] metabolites (amphetamine and methamphetamine) that may contribute to this [antiparkinson’s] effect.”³

Humbugs

The manufacturers of Sinemet (carbidopa-levodopa), the most commonly used antiparkinson’s medication, state specifically that when levodopa is combined with MAO inhibitors, a “possible hypertensive crisis”⁴ may result. Therefore, patients must “stop

¹ *Physician’s Drug Handbook*, Springfield, 2002, p. 940.

² MAO stands for monoamine oxidase. This chemical inactivates catecholamines such as dopamine, adrenaline and norepinephrine. When MAO is suppressed, these catecholamines can exceed safety levels.

³ *Physician’s Drug Handbook*, Springfield, 2002, p. 940.

⁴ *Ibid*, p. 596

Appendix 2 – Drug details

MAO inhibitors for 2 to 4 weeks before starting levodopa-carbidopa.”¹ In other words, L-Dopa should not ever be combined in any way with MAO inhibitors, including Eldepryl.

The manufacturers of Eldepryl, a drug whose only listed use is “antiparkinsonian,” fail to come right out and say that their drug should not be combined with levodopa. In fact, they imply that it is safe when they suggest that a person taking levodopa can start taking Eldepryl and then, after a few days, slowly decrease his levodopa. However, deep in the Eldepryl drug warning portion of the drug insert, one can find that Eldepryl should not be used with “adrenergic drugs.” Dopamine hydrochloride is adrenergic, and stimulates dopamine receptors of the adrenergic system. Certainly, despite the addition of carbidopa, some portion of levodopa probably also stimulates these receptors, making Eldepryl, by its own admission, unsuitable for use with Sinemet.

Dosages

10 mg per day is recommended, and never more than 10 mg/day. 5 mg should be taken with breakfast, and the other 5 mg with lunch. If a person is already taking levodopa, patients should be told to gradually decrease their levodopa dose (no suggestions as to how gradually) after 2 or 3 days of Eldepryl therapy. If, after starting Eldepryl therapy, there is an increase in adverse effects associated with levodopa, “most of these patients need a levodopa-carbidopa dose reduction of 10% to 30%.”²

Format

Eldepryl is available in 5 mg tablets and 5 mg capsules.

Adverse Effects

Eldepryl side effects can include the following long list: tremor, dyskinesia, twitching (including twitching eyelids), restlessness, loss of balance, increased bradykinesia (slowness, freezing), facial grimacing, stiffness, stiff neck, behavioral changes, loss of coordination, fatigue, headache, confusion, hallucinations, vivid dreams [including violent nightmares], anxiety, insomnia, lethargy, sleepiness, low blood pressure, high blood pressure, heart arrhythmias, palpitations, heart pain, chest pain, dry mouth, nausea, vomiting, diarrhea, constipation, abdominal pain, anorexia, weight loss, difficulty swallowing, heartburn, urinary problems (including frequency, hesitation, or retention), sexual dysfunction, skin rash, sweating, and hair loss.

Warnings

Overdose may cause symptoms such as drowsiness, seizures, coma, dangerously high or dangerously low blood pressure, and dangerous heartbeat irregularities, including heartbeat collapse. There may be a delay of up to 12 hours after the drug is taken before the symptoms of overdose appear.

Use caution if combining with alcohol, cacao (chocolate), or foods high in tyramine. These tyramine-rich foods are: cheeses, including cream cheese, bananas, meat, poultry or fish, Marmite (an English yeast product), sauerkraut, soy sauce or other

¹ *Physician's Drug Handbook*, Springfield, 2002, p. 596

² *Ibid*, p. 940.

soybean products including soy milk, beer (including non-alcoholic varieties), red or white wine, avocados, monosodium glutamate, peanuts, and raspberries.

Never use within 14 days of using Demerol. (Fatal reactions have occurred.)

Do not use with Prozac (fluoxetine). Don't start Eldepryl until at least 5 weeks after stopping Prozac, and do not start Prozac until at least 2 weeks after stopping Eldepryl.

Do not combine with adrenergic drugs. [Adrenergic drugs include Dopamine chloride, some asthma medications and epinephrine- (adrenaline-) enhancing drugs. *The Physician's Drug Handbook* has a very long list of adrenergic drugs. Please see a good drug book if you are not sure whether or not some of your medications are adrenergic.]

Never take more than 10 mg.

DEPRENYL

Deprenyl, a liquid form of Eldepryl, is advertised by its manufacturers as the "safe" alternative to Eldepryl, although the active ingredients are exactly the same. Deprenyl is illegal in the USA.

My patients who used Deprenyl had a curious effect when they stopped taking it. Both of my Deprenyl-using patients went through the typical dopamine-related drug reduction symptoms while decreasing, but when they finally got off the drug completely, they both had a highly unusual sensation as if their joints were on fire. The agonizing sensation of flame in all the joints of the body was so severe as to prevent sleep or movement. Neither patient knew the other patient, or had any information about the burning joints phenomenon. In both cases it began within two weeks of stopping Deprenyl and lasted nearly three months. This burning in the joints was unique in my experience, and occurred in addition to all of the usual depression, weakness, paranoia, insomnia and other symptoms that normally can accompany reduction of any dopamine-enhancing drug.

Deprenyl patients' background

Both patients in the above paragraph had been taking Deprenyl for several years. Both had been exhibiting symptoms of recovery for over a year before they tried stopping the Deprenyl. One had been taking a maximum of 14 drops per day, the other a maximum of 10. They both decreased slowly, over a period of two years and half a year, respectively. Neither one had ever used levodopa or a dopamine agonist, although the latter had been using Macuna and had only stopped the Macuna in the previous year. I fully expect to get strong letters stating, "Dear Madam, I quit Deprenyl and never had a moment's trouble," but please bear in mind, I am only reporting what I saw.

MIRTAZAPINE

Mirtazapine is also known as **Remeron**.

Mirtazapine was originally sold as an antidepressant. It is a member of the SSRI (selective serotonin reuptake inhibitor) family, of which Prozac is probably the most famous member. Mirtazapine is more sophisticated than Prozac: it is a dual action antidepressant. In addition to having SSRI-like properties, Mirtazapine also blocks some serotonin receptors in a manner that seems to reduce the usual SSRI side effects, and is effective over a longer time period. However, it turns out that, inadvertently, histamine receptors are also blocked. It is the blocking of the histamine receptors that causes the anti-tremor effect of Mirtazapine.

Most people who have taken antihistamines (anti-allergy, anti-runny nose drugs) will be familiar with the unfortunate side effect of supreme drowsiness. Mirtazapine, possibly due to its antihistamine (histamine receptor blocking) properties, also creates extreme drowsiness and sedation. It is this sedation that allows an anxious PDer to stop trembling while the drug is at its strongest. Mirtazapine works the same way as a nap: a nap will also stop the tremor – as long as the napper remains asleep. Mirtazapine stops tremor – as long as the user is so sedated that he is on the verge of falling asleep.

Nat, my only patient to try Mirtazapine, had to stop soon after starting it. The powerful sleepiness was effective in slowing his tremor, but he kept falling asleep while driving, and he felt mentally and physically sluggish.

Manufacturer's suggestions

As of the 2002 edition of the *Physician's Drug Handbook*, no antiparkinson's classification was yet available for this drug, and the suggested dosing was for its use as an antidepressant. When used as an antidepressant, the manufacturer suggests a starting dose of 15 mg, and a maintenance dose of 15 to 45 mg/day. Dosage adjustments should be made at least two weeks apart.

Format

15 mg and 30 mg tablets

Adverse effects

Adverse effects of Mirtazapine include severe sleepiness, dizziness, weakness, tremor, abnormal thinking, confusion, water retention, increased appetite, dry mouth, constipation, weight gain, dyspnea (breathing problems), and increased susceptibility to flu-like syndromes (due to potential for decreasing white cell count).

Warnings

Do not use together with Prozac.

Potentially fatal interactions with MAO inhibitors – do not use within 14 days of each other.

Use cautiously with people taking blood pressure lowering drugs.

Concomitant alcohol use is discouraged.

Overdose symptoms include disorientation, drowsiness, impaired memory, and slowed heart rate.

SINEMET

Sinemet is also known as **Carbidopa-levodopa**.

Sinemet is a dopamine precursor-type drug. It is made up of two parts: levodopa and carbidopa. The levodopa easily crosses the blood-brain barrier and converts quickly into dopamine. The carbidopa slows the rate at which the oral dose of levodopa is broken down by normal digestive enzymes while en route to the brain.

Manufacturer's recommendations

According to the manufacturer, "Most patients respond to 25/100, t.i.d."

A translation into English means that a pill with 25 mg of carbidopa combined with 100 mg of levodopa (referred to as 25/100), taken three times a day (t.i.d.), will give a satisfactory therapeutic response. It doesn't seem to matter whether the patient has early or advanced Parkinson's when he starts taking the medication. As long as the person has never before taken dopamine-enhancing drugs (which include many antianxiety and antidepressant meds), most people with Parkinson's, even advanced Parkinson's, will have a satisfactory response from 300 mg per day of levodopa combined with the 25% carbidopa. It may take several months to see the full benefit of the drug.

The manufacturer goes on to state that the dose may be increased every one or two days, if necessary. If using the less commonly prescribed 10/100 pills, the dosage may be one or two pills taken three or four times a day. If using the Sinemet CR (Controlled Released formula), in either the 25/100 or the 50/200 formats, the dose is two pills per day, at least six hours apart. These are merely general suggestions, however, as "maintenance therapy must be carefully adjusted based on patient tolerance and desired therapeutic response."¹

The published time frame for determining tolerance or response is three days, and yet, in the same publication, the manufacturer states that the pill can be increased every one or two days. (In case you are only reading the appendix of this book, please take a moment to read chapter three of the main text. Both of the manufacturer's thoughts on this subject may be grossly wrong.)

The Sinemet website

Sinemet is manufactured by Merck & Co., Inc., Whitehouse Station, NJ, 08889, USA, and marketed by Bristol-Myers Squibb Company, Princeton, NJ, 08543, USA. Bristol-Myers Squibb provides a website of helpful information, including "scientific studies" that are favorable to their levodopa products. Most of their scientific studies seem to have been carefully selected to encourage use of levodopa as soon as possible after a patient is diagnosed. They also seem to contradict the overwhelming majority of recent levodopa studies, mentioned nowhere on this website, that show a clear advantage to delayed use of levodopa when compared to starting levodopa therapy as soon as possible.

Website (www.sinemetcr.com/cross_site/CurrentSinemetCRPI.pdf)²

¹ *Physician's Drug Handbook*, Springfield, 2002, p. 596.

² Their website supposedly gives information about either the regular Sinemet, or the Sinemet CR. However, whether you click on the website to request the regular Sinemet information or Sinemet CR info, only the Sinemet CR page appears. I was not able to actually find a regular Sinemet page, only the CR

Website points of interest

“Sinemet CR may cause more dyskinesias than Sinemet. The occurrence of dyskinesias may require dosage reduction...”

“A dose of Sinemet 25-100 or 10-100 (one half or a whole tablet) can be added to the dosage regimen of Sinemet CR in selected patients with advanced disease who need additional immediate-release levodopa for a brief time during daylight hours...”

“When doses are not equal size during the day, it is recommended that the smaller doses be given at the end of the day...”

“An interval of at least 3 days between dosage adjustments is recommended.

“Sinemet CR should not be chewed or crushed...”

“Carbidopa inhibits vitamin B6.”

Website tips on mixing levodopa with other drugs

“There have been rare reports of adverse reactions, including hypertension [high blood pressure] and dyskinesia, resulting from the concomitant use of tricyclic antidepressants and carbidopa-levodopa preparations...”

“Postural hypotension has occurred when carbidopa-levodopa preparations were added to the treatment of patients receiving some antihypertensive drugs. Therefore, when therapy with Sinemet is started, dosage adjustment of the antihypertensive drug may be required.” A translation into English might read: dizziness or passing out when changing from a sitting to a standing position has happened with patients taking blood pressure medications together with Sinemet. Because Sinemet can lower the blood pressure, sometimes the blood pressure medication needs to be decreased to prevent passing out...

“Concomitant therapy with selegiline [Eldepryl] and carbidopa-levodopa may be associated with severe orthostatic hypotension not attributable to carbidopa-levodopa alone.” (A translation of this one might be: combining Eldepryl and Sinemet can cause severe passing out when changing from sitting to standing. If this very bad result occurs, don't blame the levodopa, blame the other drug.) Again, this information is from the levodopa website...

“Anticholinergic agents, dopamine agonists, and amantadine can be given with Sinemet. Dosage adjustment may be necessary when these agents are added.”

Format

Regular Sinemet, also known as quick release or fast acting Sinemet, is available in 10/100, 25/100, and 25/250 tablets. (The smaller number tells how many milligrams of carbidopa are in the pill, and the larger number is the measure of levodopa. In calculating how much levodopa one is taking, it is the larger number that should be used.)

A slow-release tablet is available in CR 25/100 and CR 50/200. The letters CR merely refer to the slow release (Controlled Release) construction of the tablet; the active

page. Some of the Sinemet CR page is oriented towards teaching doctors how to do a conversion from regular Sinemet to Sinemet CR. It is interesting to note that the patent has expired on regular Sinemet. Some cynics have noted that, although the CR technology was available years earlier, the CR pills were not released on the market until the patent on the regular Sinemet was nearly ready to expire.

ingredients of the pill are exactly the same in the CRs as in the regular pills. The same side effects and warnings apply to both the regular and the CR.

Known adverse effects

A *partial* list of the adverse effects from levodopa includes: tremor, dyskinesia, dystonia, choreiform [jerky, spasmodic movements, another way of saying “dyskinesia”], facial grimacing, head movements, muscle twitching, body jerks, ataxia [inability to coordinate muscle movements], bradykinetic episodes [slowness of movement, freezing], psychiatric disturbances, anxiety, euphoria, excessive salivation [drooling], choking, malaise, fatigue, severe depression, suicidal tendencies, dementia, delirium, hallucinations, confusion, echolalia [repeating a word (usually rapidly), particularly a word that someone else just said, over and over], agitation, heartbeat irregularities, lowered blood pressure, double vision, blurry vision, dry mouth, bitter taste in the mouth, nausea, vomiting, anorexia, constipation, diarrhea, abdominal pain, urinary frequency, urinary retention, incontinence, darkened urine, priapism [persistent, often painful erection in the absence of sexual interest], decrease in red and/or white blood cells, liver problems, weight loss, hyperventilation, hiccups, unusually fast speech.

Symptoms of overdose

“Muscle twitching, including twitching of the eyelids, and heart arrhythmias [irregular heart rate, angina, heart pain] may be signs of overdose.”¹ Treatment of overdose includes stomach pumping and treatment for the heart arrhythmia, if needed.

Warnings for patients

“Maximum effectiveness of drug may not occur for several weeks or months after therapy begins.”²

(The instructions for pure levodopa, unmixed with a buffer such as carbidopa (trade names Dopar and Larodopa), state that it may take six months for the full therapeutic response to appear.³)

Monitor carefully any patient who is also taking medicine to regulate blood pressure or blood sugar.

Patients on long-term therapy should be tested regularly for diabetes, liver and kidney function, and acromegaly.

“Tell patient to take food shortly after taking drug...” to relieve stomach irritation.

“Patients should take a missed dose as soon as possible, but should skip a missed dose if the next scheduled dose is within 2 hours, and never double the dose.

“Elderly patients are especially vulnerable to central nervous system adverse effects such as anxiety, confusion or nervousness; those with preexisting heart disease are more susceptible to cardiac [heart] effects.”⁴

Levodopa should be stopped 6 to 8 hours before administration of anesthetic drugs or hydrocarbon inhalation.

¹ *Physician's Drug Handbook*, Springfield, 2002, p. 597.

² *Ibid* p. 597.

³ *Ibid* p. 595.

⁴ *Ibid* p. 597.

Appendix 2 – Drug details

MAO inhibiting drugs (these include Eldepryl) should be stopped 2 weeks before starting levodopa-carbidopa therapy.

Contraindications

Patients with acute angle-closure glaucoma, melanoma, undiagnosed skin lesions, or those who have used MAO inhibitor drugs within the last 14 days should not use this drug.

I have not been able to locate the study that led to the contraindication of Sinemet in the presence of melanoma (a deadly skin cancer). It is interesting to note that several of my patients have had skin cancers removed from their face after starting with Sinemet. However, since Parkinson's disease involves an absence of Qi in the face, and cancers can grow where there is an absence of Qi, it may be that the Parkinson's, and not the Sinemet, is responsible for the melanoma. It is possible that, since western MDs assume PD to be only an illness of brain cells, and most PDers of the last few decades are on Sinemet, their incidence of skin cancer has been wrongly attributed to their medication.

A Sinemet case study

Mark was diagnosed with Parkinson's disease at age 58. He started our program ten years later. At that time he was taking Sinemet 25/100 three times a day and Artane twice a day. He had tried adding Mirapex when the Sinemet decreased in effectiveness, but the combination of Mirapex and Sinemet caused dyskinesia. Mark's wife of thirty-six years, Margaret, was more alarmed by the facial grimacing and dyskinesia than she was by Mark's increasing immobility.

Dr. Rafferty, assuming that the dyskinesia was due to levodopa going into the body and not the brain, added Comptan to the mix. The Comptan increased the dyskinesia. They tried stopping the Mirapex while continuing with Comptan, but the dyskinesia continued. Just before joining our project, they stopped the Comptan as well. After his experiments with Mirapex and Comptan, Mark was no longer getting good results from his Sinemet, but he now had facial grimacing and mild dyskinesia within an hour of each dose; he had the side effects but not much benefit from his Sinemet.

Immediately upon entering our program, Mark started reducing his medication. Margaret took charge of his drug doses. Her plan, which Mark agreed to, was a 10% reduction every two weeks. When the daily amounts were so small that it was unreasonable to reduce by a daily 10%, she reduced by a weekly 10%. When Mark got down to 100 mg/day, she started reducing by 50 mg/*week*. She made a reduction every two weeks, come hell or high water.

A plan with flexibility

Sometimes she had to accelerate her plan; Mark responded well to the PD recovery treatments and his dyskinesia worsened, despite the reductions. She used his tendency toward facial grimacing or dyskinesia about an hour after his doses as her litmus test for accelerated drug reduction: whenever the dyskinesia reappeared, Margaret made another slight reduction, even if it was ahead of schedule. Within a few days or a week of a drug decrease, the dyskinesia would usually stop and Mark would go into a slump. If this was the case, Margaret still held to her 10% plan: sometimes it seemed as if he was still declining into drug reduction symptoms when it was time to make the next

reduction. Even if he was in a phase of feeling worse every day, Margaret stayed the course and Mark made another reduction. Other times he rebounded within days from a drug reduction: he was moving well or even having dyskinesia again less than two weeks after making a reduction. In these latter cases, Margaret made another reduction, ahead of schedule.

If Mark became too listless, Margaret reduced the Artane (anticholinergic). If the dyskinesia reappeared, the Sinemet was decreased.

There was no obvious pattern as to which reductions would send Mark into a tailspin and which ones would go easily. However, Mark's behavior followed predictable patterns. When he started having feeling in his feet, he became clinging and needy. When he started urinating every ten minutes throughout the night, he also became fearful of being alone. About two and a half months after the first decrease, he became angry and threatened violence unless Margaret allowed him to increase his pills.

The week before his first violent outburst, I had suggested to Margaret (out of Mark's hearing) that he was approaching the time when he might get hostile. When he did become angry and threatening, she was emotionally prepared. She laughed him off, told him that he was behaving according to prediction, and kept with her drug program. Shortly after this, I warned her that Mark seemed ready to collapse into infantilism. During the following week, he started crying, whimpering, and – for the first time in his life – talking about his grandmother, the only person who had ever really nurtured him.¹

A temporary increase

At one point, Mark became adamant that he needed to increase his medication – his legs were turning limp and would not support him. He was severely disappointed when the weakness appeared – the week before he had been able to get in and out of the car easily, even gracefully, for the first time in years. He had hoped that this increased mobility had meant he was recovering, which it probably did, but when the subsequent limpness and weakness appeared, he went into a profound emotional slump. I suggested that since limpness was a symptom of recovery, an increase in his medication might cause an increase in dyskinesia with no corresponding increase in mobility. However, his dependency over his immobility was so great that Margaret did increase his medication. Within two days his dyskinesia was back with a vengeance and appearing sooner than

¹ While it is impossible to predict on paper just when a person will go through various phases of recovery and drug withdrawal, it was enormously gratifying to work with Mark and Margaret and see that my years of working with patients had indeed given me a reservoir of subtle cues so that I could almost sense when a person was going to have a change. While this may not be of help to the reader, it did help confirm to me that there is some sort of sequence and predictability, even in the timing and patterning of these complex stages. While I cannot yet categorize them or give written prediction/instruction to others in this book format, by working closely with these people it became evident to me that people in conditions of drug reduction or recovery do behave in a highly predictable pattern, if one can mentally integrate all of the incoming behavioral data. Just as a child living with a “crazy” parent can learn just when and under what conditions “mom is going to blow,” even though to an observer the behavior seems random, I found that after four years of working with people reducing their drugs, there were dozens of subtle signals that allowed me to guess fairly accurately whether or not a reduction might be difficult or easy, and to predict just which emotional aspects might go haywire during the upcoming week. Try as I might, I still cannot find a way to take the basis for these successful “guesses,” built on years of personal experience and learning, and convert it into written information.

Appendix 2 – Drug details

before, a mere 45 minutes after the dose. He was still unable to get up out of a chair, even when he was grimacing. He then agreed to continue with the reduction.

Off the drugs

They started the drug reductions in early April and Mark was off his medication on the 4th of July, Independence Day.

Back on, two weeks later

Mark declined rapidly after he stopped the Sinemet. After two weeks of increasing shakiness, utter insomnia, terror at being alone, needing to be helped out of a chair every five minutes and then needing to be returned to the chair, mental and physical agitation combined with moments of utter physical helplessness, long periods of freezing, terrific stabbing pain and cramping in his legs that did not respond to heat, massage, or his nightly rum, he resumed Sinemet, with Margaret's blessing and mixed emotions.

Margaret felt like a failure because he was taking Sinemet again. I pointed out to her that most people who completely stop taking Sinemet have two or three bouts during which they get back on it again, have worse side effects than before, stop taking it, feel horrible, get back on, have even worse side effects, and then, sometimes, get off for good. Getting completely off the meds is a glowing goal, but after the goal is attained there is a post-victory crash, and the looming years of recovery are so daunting that resuming the medication, maybe temporarily, is pure routine: most people do it. My job at this time was to remind them both that they needed to do whatever was best for them and never to feel like failures.

Getting outside help

Within a month of starting the Sinemet reductions, Margaret would repeat to me nearly every week in the clinic, "You told me this would be the hardest thing I've ever done, and I believed you, I was ready for it. But I never knew just how hard "hard" could be."

Margaret asked for and received help. She asked Mark's brother to come over and sit with Mark so that she could get out of the house. This was particularly helpful; Mark's brother refused to yield to Mark's every request and gently made fun of Mark when he slid into self-pity. Mark quickly learned, even in his drug-reduction confusion, that he could be demanding of Margaret but not of his brother. It was very helpful for Margaret to learn that. After that, she started discriminating between the help that Mark wanted and the help that Mark needed. She did what she needed to do to keep her sanity. She got out of the house, she gave Mark rum and big meals to make him sleep a few hours at night, and whenever he slept, she slept. Margaret reported that caring for Mark during this time was more like having an infant in the house than a spouse.

Off the drugs, again

After two weeks of taking either 50 or 100 mg/day of Sinemet, during which time he continued to agonize due to recovery symptoms, Mark stopped taking Sinemet altogether. Margaret felt that since he was just as agitated with the medication as he was without it, they would see what happened after a few months with no medication. Mark

continued to go into a decline. Margaret referred to the next few months as “hell. Pure hell. I’m exhausted. I’m ready to kill him. Seriously.”

Skin cancer

During this time he had a serious setback. He was just starting to feel mildly better, now and then, and his old, pre-PD sense of humor and quick wit was starting to shine through, when his doctor diagnosed the sores on his nose and face as skin cancer. When he received this diagnosis, he became completely immobilized, losing any mobility progress he had made. His mood collapsed and he was utterly helpless. The cancers turned out to be superficial. The dermatologist burned them off and announced that they were completely gone: the removal had been a complete success. However, whenever Mark looked in the mirror during the next few weeks, he saw a face disfigured with seven angry red scabs, and his depression deepened.

However, as the scabs started to fall away, he started to feel hopeful again. On October 31, exactly three months after taking his last Sinemet, his mood brightened considerably and his personality returned. Margaret wrote, “The addiction hell is over.”

Sleeping through the night

Mark remained prone to restlessness and agitation through November. At the end of the first week of December, 18 weeks after taking his last Sinemet, Margaret announced that he had turned a corner: he could sleep through the night, and he was no longer freezing.

His personality had returned, enriched by the newfound emotional sensitivity that many recovering PDers say is “worth the price of having had Parkinson’s.” At this time his Tui Na practitioner said, “Lately I feel like I’m treating Mark; I used to feel as if I was treating a mound of twitchy drugs or else the drug withdrawal, and that Mark was buried somewhere inside.” Margaret said, “I’ve got my husband back.” Mark said he could not have done it without Margaret.

A few more Odds and Ends about Sinemet

Breaking pills

The regular pills and the Sinemet CR 50/200 can be broken in half with no alteration in speed of effectiveness. The CR pills lose their slow-release property and become very fast acting if they are chewed or crushed. Some patients know almost nothing about their Sinemet CRs except that the pills should *never* be crushed or broken. Based on their misinterpretation of the drug brochure, most patients assume that dire side effects or utter pill failure will occur should they ever accidentally ingest a pill that has been broken. This is incorrect.

What happens if the pill is carefully broken (as opposed to smashed) is this: the *slow-release coating* and internal structure of the pill is slightly compromised. When this happens the CR pill works slightly more quickly than usual. The broken CR doesn’t work as quickly as a regular pill, of course, because even if the pill is broken a considerable portion of it still maintains the slow-dissolving structure. The breaking of a CR pill does not effect the properties of the drug or in any way alter the active ingredients; breaking a

Appendix 2 – Drug details

CR merely compromises the slow-release feature so that the CR dissolves at a rate somewhere between that of a regular Sinemet and an unbroken Sinemet CR.

Crushing the pill, on the other hand, makes the entire contents of the pills available at once; the result is an overfast surge of drug. Neither the regular nor the CRs should be crushed.

Vitamin confusion

Conflicting evidence about vitamin B6 abounds. According to the Sinemet manufacturer's website, carbidopa prevents inhibition of levodopa digestion by inhibiting vitamin B6 from digesting levodopa. Products that contain vitamin B6 can reduce the effectiveness of levodopa, according to the makers of pure (non-buffered) levodopa. However, the *Physician's Drug Handbook*, based on information provided by the manufacturer, states that vitamin B6 does not reduce the effectiveness of carbidopa-levodopa (Sinemet). It states, "Multivitamins can be taken without fear of losing control of symptoms." Given the conflicting evidence of the authorities, and my lack of experience in this area, you are on your own with this one.

Comparing the 10/100 and the 25/100 formulation

Although the 25% ratio of carbidopa to levodopa is the one most frequently used by patients in our experience (25/100 or 50/200), we have seen one person using the 10% carbidopa (10/100 or 25/250) formulation. Because some people do not tolerate carbidopa well, this pill may possibly be made for those few individuals. However, the one person we knew who was taking the 10% pill was taking it because his doctor chose it at random. The 10% pills have less carbidopa and therefore offer less protection to the levodopa molecule as it tries to make its way past the digestive engines and into the blood. Therefore, the amount of levodopa that makes it into the bloodstream may be less with the 10% pills, depending on the total amount of carbidopa ingested during the day. It is impossible to know just how much less dopamine is available when comparing the 10% pills and the 25% pills: everyone's digestion is different.

The manufacturers suggest that the 25% buffered pills yield 4 times more levodopa to the brain than the completely non-buffered pills. No information is readily available about the relative dopamine yield of the 10% (partially buffered) pills.

Another factor that must also be borne in mind is that the body is supposedly saturated with carbidopa after 70 mg of carbidopa per day. This means that after the first 70 mg of carbidopa of the day have been taken, the rest is simply excess. Therefore, at doses higher than seven pills of 10/100 carbidopa/levodopa, the effectiveness of the levodopa portion of the pill is comparable to that attained after taking three 25/100 pills. At doses lower than seven pills a day, the effectiveness of the carbidopa in the 10% pills may be significantly lower in the 10% pills than in the 25% pills.

Don't forget: although the manufacturers throw the "70 mg" number about as if it were etched in stone, it is only an average number; individuals might vary widely in their response to carbidopa.

One has to wonder about the accuracy of the statement that 70 mg per day provides full saturation of carbidopa. For starters, if this is the case, and if the starting dose of Sinemet CR is 50/200, twice a day, this means that the starting dose is more than the body can absorb. Any increase would be pure excess, pure waste, in terms of the

carbidopa. One has to wonder why the manufacturers are shoving such high levels of carbidopa into the pills if anything over 70 mg/day is wasted. It is a mystery.

Buzz

Throughout this book, except in the case study of Buzz (chapter 23), all dopamine numbers are based on the 25% carbidopa/levodopa pills. Buzz was taking the 10/100's. Therefore, if you are trying to understand what happened with Buzz when he abruptly quit his medication, you must bear in mind that his brain may have been receiving, post-digestion, only a fraction (probably somewhere between a fourth and a half) as much levodopa as a person would have been getting from the more common 25% formulation. Actually, although the manufacturers state (based on what level of testing I do not know) that 70 mg/day of carbidopa is the saturation point, I have to look at Buzz and wonder if possibly he was receiving quite a bit less levodopa than a person taking the 25% format. If so, this might explain his "ease" during drug reduction, compared with all the other drug users: he was possibly absorbing much less levodopa than most.

Final report on Mark and Margaret

Recently (May 10, 2003), I received an emailed notice that Mark had passed on. I had been out of the area since mid-December when he "turned the corner." I had not seen him since starting work on this book in January; my only information on him was in emails from his acupuncturist.

Briefly, the end of his story is this:

In late December, Mark's basal cell skin cancer reappeared. The reappearance of the cancer was an emotional blow and he took it very hard: his father had died of cancer.

He began what Margaret called "massive" radiation treatments several times a week. Margaret said that the radiation seemed to take a lot out of him; he grew weaker in response to each treatment. In mid-April, he started having uncontrolled diarrhea. After more than a week of constant diarrhea and the beginnings of fever, Mark went into hospital. The diarrhea continued, the fever worsened and he was diagnosed with pneumonia. He was barely aware of his surroundings. After twelve days in hospital, Margaret insisted that he be brought home. He was aware that he was home, and seemed grateful to be there. His heart rate and breathing gradually slowed. He peacefully passed on, eight hours after returning home. His son and Margaret were by his side.

Margaret volunteered to me that, despite the hellish hardships during Mark's emancipation from drugs, they were glad to have been in the clinic program. She told me, "We had no regrets. We did it out of hope and optimism. We never gave in to Parkinson's."

Mark's brother, who had often sat with him during the worst of the drug withdrawal, was grateful that Mark had won through the challenge of drug reduction. After Mark's passing, the brother thanked Margaret for her valiant struggles during Mark's drug reduction the previous year. He said, "You gave him this time, this last year, of not being stoned on drugs."

