UNUSUAL MEDICATION REGIMENS IN THE TREATMENT OF DISSOCIATIVE DISORDER PATIENTS: PART I: NORADRENERGIC AGENTS

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The unusual medication regimens described in this paper are reported in the context of experimental protocols, and should not be viewed or adopted as accepted clinical practice.

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ABSTRACT

The noradrenergic agents propranolol, and to a lesser extent, clonidine, are used in an experimental setting to reduce switching and anxiety in dissociative disorder patients, making them better candidates for psychotherapy. The rationale for this non-FDA-approved use of the drugs is founded in the James-Lange and Cannon-Bard theories of emotion. It is hypothesized further that the mechanisms proposed by the two theories are reinforcing of one another via classical conditioning in the production and reinforcement of chronic, severe anxiety responses. The effect of propranolol and clonidine can complement the effect of benzodiazepines in these patients. In the experimental protocol described, propranolol or clonidine is sometimes used at ultrahigh doses, with patients always under close medical supervision.

INTRODUCTION

Racing, fragmented, disordered thought processes and/or rapid switching are commonly encountered features of Dissociative Disorder NOS (DD NOS), and of multiple personality disorder (MPD) in particular. Effective psychotherapy is difficult to accomplish in these patients when their thought processes are so disarrayed. Psychopharmacology alone is not the answer to this problem, but psychoactive medication can be successfully used to reduce ancillary symptoms such as depression, anxiety, rapid switching, and sleeplessness. Medication serves as an adjunctive aid to facilitate psychotherapy. Two drugs, propranolol and clonidine, have been particularly effective to help in the treatment of anxiety, impulse discontrol, and rapid switching.

Propranolol is a competitive beta-adrenergic receptor blocker that is used primarily as an anti-hypertensive agent and for migraine headaches. Clinical observation and experi-mentation over several years have indicated that propranolol offers a very useful pharmacologic approach to help control rapid switching in MPD patients. Other drugs may be useful in supplementing or complementing propranolol's action, but in my experience, propranolol in large to ultra-large doses appears to be the agent of choice. Over a five-and one-half year period, I have conducted an open trial of propranolol (without a control group) with more than 100 severely incapacitated dissociative disorder patients. These patients were on an average regimen of 800 mg of propranolol per day, ranging from approximately 300 mg to an extreme of 1600 mg per day. The longest duration of propranolol usage was four and one-half years. This patient and two others who received 1200 mg or more per day are currently off propranolol and all other medications. They have been functioning well for approximately one year.

The propranolol and clonidine regimens discussed in this paper describe the use of FDA-approved medications for non-FDA-approved purposes at higher than FDA-approved doses. Informed consent *must* be obtained from patients and appropriate notations must be made in patients' charts, including an indication that the patient understands and gives consent. Even more important than consent is a thorough knowledge of the medication and its pharmacokinetics, and the close monitoring of the patient's vital signs and the medication's side effects.

HISTORY AND RATIONALE

Benzodiazepines were previously the agents most successfully used to calm thought processes and decrease switching in MPD patients at the Dissociative Disorders Program, Rush-Presbyterian-St. Luke's Medical Center, Chicago. The most commonly used agent, which also appeared to give the best results, was the benzodiazepine alprazolam, characterized by its dose-related central nervous system activity. At high dosage levels of alprazolam, results were satisfactory in

many patients, but still were not as consistent or as good as I had hoped to see.

The use of propranolol and clonidine in patients with post-traumatic stress disorder (PTSD) was brought to my attention by an article on this subject by Kolb, Burris, and Griffiths (1984). Although the authors found these drugs to be somewhat useful at the doses up to 160 mg of propranolol or 0.4 mg of clonidine per day, the results were not promising enough to encourage them to pursue intensive research. However, the idea of using a beta-adrenergic blocker or an alpha$_2$-adrenergic agonist for MPD was intriguing. I had been looking for a medication regime that would improve upon the results from benzodiazepines. Theoretically, the use of these medications made sense within the context of a hypothesis which combined concepts from the Cannon-Bard (1927) and James-Lange (1934) theories of emotion with concepts from Pavlovian conditioning (Pavlov, 1927).

The Cannon-Bard theory of emotion (1927) states, in essence, that one feels anxious as a result of anxiety-producing thoughts. The physiologic result of these thoughts are increased ventilation, tremulousness, muscle tightening, increased heart rate, etc. This concept proposes that our emotions start centrally (thought) and are followed by peripheral (physiologic) effects.

The James-Lange theory of emotion (1934) reverses this concept by proposing that physiologic symptoms are interpreted by the brain as anxiety or fear. For example, if one is walking down a flight of stairs and trips, there is no time to *think* about the danger. Instead, one reacts reflexively, catches him/herself, then feels tremulous with a pounding heart, etc., which is interpreted as anxiety or fear.

The Cannon-Bard (C-B) and James-Lange (J-L) theories of emotion interact with one another in mutually reinforcing ways. Either mechanism can initiate anxiety. Triggering anxiety centrally via associations and/or environmental stimuli (C-B) activates peripheral tremulousness, tachycardia, etc. These physiologic symptoms foster the central recognition of anxiety and further exacerbate the peripheral symptoms, creating a circularly escalating anxiety. Peripheral (J-L) activation by exercise or an environmental stimulus can be so subtle as not to be recognized and brought to consciousness, although the brain recognizes the peripheral symptoms and often perceives them as anxiety.

Using concepts from Pavlovian conditioning one can understand how a patient suffering from chronic anxiety can spiral into even greater anxiety (see Figure 1). For example, a child who was repeatedly abused in a yellow room responds to a yellow room with tachycardia. The color, as it appeared on the walls during the abusive episodes, was at first a neutral stimulus (NS). With repeated episodes the neutral stimulus becomes associated with abuse, the unconditioned stimulus (UCS). Over time, the color seen in other environments becomes the conditioned stimulus (CS), the cue which triggers anxious thoughts able to elicit tachycardia, the conditioned response (CR) without the child abuse. This is, in essence, a Pavlovian description of the Cannon-Bard theory. Using a similar Pavlovian approach to the James-Lange theory, the color yellow is responded to with tachycardia which serves as the conditioned stimulus to activate thoughts of anxiety. Thus, it is apparent that these two systems mutually reinforce one another.

This circularity of classically reinforced anxiety would appear to explain why the use of benzodiazepines alone were insufficient to break the fear/anxiety cycle in our chronically, severely anxious patients. Benzodiazepines work in the brain as GABA agonists, decreasing anxiety by their effect on calcium influx and membrane potential that decreases the firing of the nerve cell. Propranolol, on the other hand, diminishes the peripheral symptoms of anxiety, tremor and tachycardia by decreasing the effect of norepinephrine post-synaptically through competitive blocking of the beta receptors. Clonidine, an alpha$_2$-receptor agonist, acts pre-synaptically upon the noradrenergic system. It stimulates the alpha$_2$-adrenoreceptor to decrease the amount of norepinephrine available at the synapse, and decreases the sympathetic outflow from the autonomic nervous system. The use of benzodiazepines in combination with propranolol and/or clonidine reduces anxiety via both the GABA system (Braun, in preparation) and the noradrenergic system.

CHOOSING PROPRANOLOL

In experimentation with drugs and dosages, one must always be cognizant of the unique and often unpredictable hazards of pharmacotherapy in MPD patients (Barkin, Braun, & Kluft,1986; Braun, 1983; Kluft, 1984; Putnam, Guroff, Silberman, Barban, & Post, 1986; Putnam, 1989). An individual patient's alters may have different responses to the same medication. In using an experimental therapy in MPD patients, it is essential to obtain informed consent before therapy is initiated (Braun, 1984; Putnam, 1984; Braun, 1986). This may require explaining everything more than once. Further-more, in MPD patients as a group, side effects appear to be less clearly dose-related than other psychiatric patients (Putnam, 1989).

Kolb, et al. (1984) pointed out that either the alpha$_2$ agonist clonidine or the beta-competitive antagonist propranolol decreases the amount or the effectiveness of norepinephrine at the synaptic cleft, thus reducing the firing of the next cell in line. Although initially clonidine was tried, thinking that it was safer, the first few patients observed could not tolerate its sedating side effects. Propranolol was then attempted, and had the advantage of more rapid onset of action over clonidine and less sedation. In addition, propranolol dosage could be titrated more closely and it had less sedating side effects. Early patients' doses were raised quite slowly and no effect was seen until at least 240 mg was reached. With experience, a more rapid regimen was developed, as discussed below.

Propranolol is a synthetic beta-adrenergic receptor competitive blocking agent with no other autonomic nervous system activity. Because there is no simple correlation between dose and therapeutic effect, the adjustment of clinically effective dose requires titration. A wide dose-sensitivity range is observed in clinical use of propranolol for management of hypertension and other FDA-approved indications. This is also true of its use to control symptoms of fragmented, disordered thoughts and rapid switching in the MPD patient.

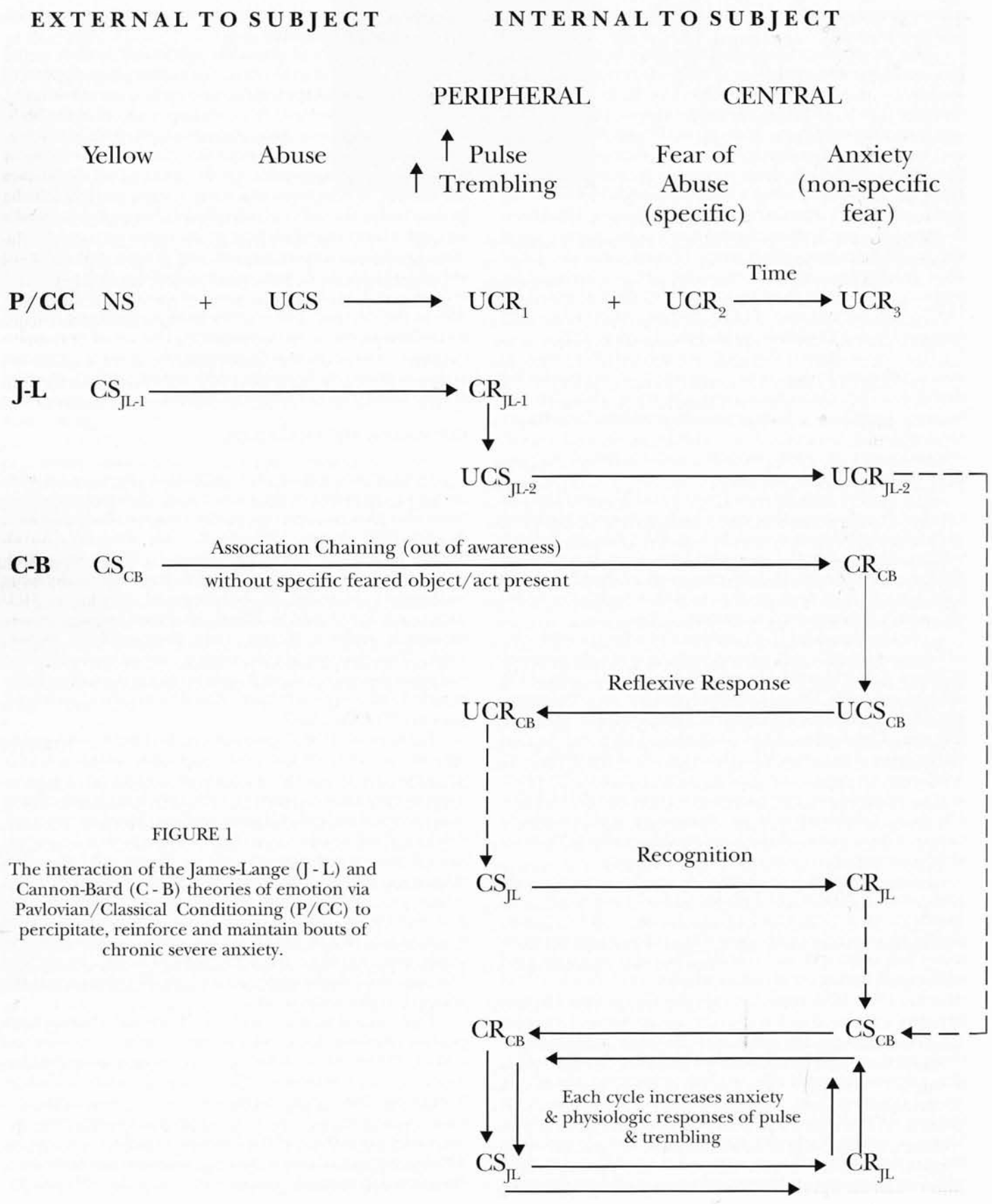

FIGURE 1

The interaction of the James-Lange (J - L) and Cannon-Bard (C - B) theories of emotion via Pavlovian/Classical Conditioning (P/CC) to percipitate, reinforce and maintain bouts of chronic severe anxiety.

The neuropsychological effects of beta-blocking agents are not well defined or understood, but are well documented (Gershon, Goldstein, Moss, & van Kammen, 1979; Meibach, Cunner, Wilson, Ishiki, & Dager, 1987; Cole & Koob, 1988; Dimsdale, Newton, & Joist, 1989).

Propranolol's approved indications include the management of hypertension, long-term management of angina pectoris, reduction of mortality after myocardial infarction, prophylaxis of migraine, and management of essential or familial tremor.

For dissociative disorder patients, in our experience, the indication for the use of propranolol is rapid for uncontrolled switching. Switching is usually precipitated by severe anxiety, fear, various environmental stimuli, or their interactions with the patient's life experiences.

Another advantage of propranolol is that its use often reduces the amount of benzodiazepines needed, and therefore reduces their potential to disinhibit and unleash violent behavior. A related advantage is propranolol's ability (at significant doses) to inhibit impulsive behavior.

The drug's contraindications include situations where sympathetic stimulation is required and vital – e.g., (1) bronchial asthma, (2) sinus bradycardia, (3) greater than first degree heart block, (4) congestive heart failure, (5) insulin-dependent diabetes, and (6) Raynaud's disease. Any suggestion of bronchial asthma in a patient is an indication for pulmonary function testing prior to administration of propranolol. Work presented by Khan and Braun (1989) suggests why propranolol has had good success in MPD patients previously diagnosed as having asthma. It was found that these patients had an upper airway disorder that appeared to be asthma, but was not.

Propranolol is known to mask hyperthyroidism, and to change thyroid function tests, especially for the breakdown of T_4 and T_3. My colleagues and I have seen one patient in whom propranolol therapy caused an apparent hypothyroid condition over a six-week period. When admitted to another hospital the T_3 and T_4 tests were at upper limits of normal; after a six-week course of propranolol, T_3 was at lower limits of normal and T_4 and TSH were normal.

Attempts were made to mimic the effects of propranolol on symptoms with the cardioselective $beta_1$ blocker atenolol with a very limited success. Atenolol, unlike propranolol, does not penetrate the blood-brain barrier. At higher doses propranolol appears to have both peripheral and central effects, and the central effects appear to involve the locus ceruleus, the lymbic system, and perhaps the frontal lobe. Thus, use of a drug that crosses the blood-brain barrier is probably essential for the best results.

Another attempted modification was the use of metoprolol a $beta_1$-antagonist, which has effect on peripheral target symptoms but does not greatly effect the respiratory system. Though it is believed that 50 mg of metoprolol equals 80 mg of propranolol, comparable doses of metoprolol to propranolol appear to be somewhat less effective in controlling psychological symptoms such as rapid switching. In addition, it appears that in doses greater than 200 mg/d metoprolol it loses its $beta_1$-selectivity. However, there are times when metoprolol is indicated: I am currently treating an eight-year-old boy with 150 mg/d of metoprolol after his original good response to propranolol was complicated by respiratory problems.

CURRENT DOSAGE MANAGEMENT

The obtaining of informed consent for the use of propranolol in the pharmacotherapy of dissociative disorder patients is mandatory. For example, the patient is told that s/he will receive an FDA-approved medication for a non-approved use (to decrease dissociative episodes) in excess FDA-approved dosages. It is then explained that, in the experience of our unit, propranolol decreases the rapidity of the switching process, but does not prevent switching. Thus, a person who switches less frequently is more in control, and is better able to engage in psychotherapy. One of the major listed side effects of propranolol is the slowing of thought processes. This, however, is the effect that is being sought out in our usage. The effect of lowering of blood pressure is, in my opinion, the major side effect in the use of propranolol described here. This side effect, depression, and others described in the Physician's Desk Reference (PDR) (1990) and elsewhere require careful monitoring and are explained to the patient. After discussing the advantages, risks and side effects, a notation is made of this discussion in the patient's chart, making certain to add that the patient was competent, understood the information s/he received, and concurred with the decision to administer the medication. Of course, one can only make such an entry if one is certain that this is true. The patient must be strongly admonished against rapidly discontinuing this medication, and warned that rapid discontinuance is associated with risk of cardiac arrythmias and a hypertensive rebound.

On the Dissociative Disorders Unit at Rush North Shore Medical Center, orthostatic (sitting and standing) blood pressure and pulse readings are taken before every dose of propranolol or clonidine. A dosing schedule is instituted after baseline blood pressure and pulse are obtained. These are used to establish parameters for withholding propranolol. Propranolol is withheld if blood pressure or pulse go below the parameters. For outpatients the parameters are set higher and dosage increase is undertaken at a maximum of one-half of the inpatient rate. An inpatient is usually started on propranolol at a dose of 10 mg four times a day. The aim is to administer a total daily dose of 40 mg to the patient on the first day. If the first dose is given in late afternoon, I give two 20 mg doses to meet the 40 mg first-day schedule. Also, a 10 mg dose of propranolol Q3-4 hrs prn may be useful.

On the following day, our experience indicates that total dosage may be increased to 80 mg (20 mg q.i.d.). On the third and successive days, doses are increased by 10 mg q.i.d. (40 mg/day) until the total daily dosage reaches 600 mg (see below). If the blood pressure and pulse are well above parameters the inpatient rate of dose increase can be increased slightly faster, based on the amount of prn medication taken. In our experimental protocol we add 40 mg to the total (regular and p.r.n) dose received the previous day, (as 10 mg q.i.d.) when more rapid increases are needed to help control a very difficult patient.

At the 600 mg-per-day level, dosage is increased by 10 to 20 mg per dose at a rate of 40-60 mg per day until the total daily dosage reaches about 800 mg. Afterwards, the dosage is increased by 60-80 mg per day, at 10 to 20 mg per dose. This increase is pharmacologically justifiable because the increase is only 10% or less of total daily dose. Preliminary studies are underway to define effective blood levels.

In our protocol the medication is given provided that any one of the following parameters is not exceeded. Others wishing to use such regimens should work in consultation with an internist and establish parameters consistent with the medical assessment of each unique patient.

(1) Blood pressure falls below acceptable levels (a decrease of 20mm Hg or more systolic and 12mm Hg or more diastolic from baseline). In a patient whose BP is normally about 100/70, a drop to about 80/60 can be tolerated; if the normal pressure is about 90/60, a safe parameter seems to be 78/55. At levels below these, medication is held or withdrawn at an appropriate rate.

(2) Pulse rate falls below acceptable levels, a maximum of 20 beats per minute from baseline for the first parameter established. This can be adjusted downward over time. In a patient whose pulse rate is normally about 76, a pulse of 56 is usually well tolerated; after a patient has been on propranolol for a time, one may accept a pulse rate of 52.

(3) Orthostasis is seen as represented by a systolic drop of more than 20 points, a diastolic drop of more than 10 to 15 points, and/or the pulse increasing by more than 20 beats per minute, when the pressures/pulse are taken sitting and then standing.

Several patients have been on sustained daily doses as high as 1200 mg to 1600 mg/d plus p.r.n. medications. Exercise tolerance is somewhat limited, but sexual performance has not generally been as limited as one might presume. One female patient engaged regularly in sex with her husband while she was receiving 1200 mg of propranolol daily, and a male patient on 1400 mg per day has reported no sexual problems.

Increases in dose are continued in our experience until one of the following two events is seen: (1) Switching is decreased to a level where the patient is calmer and better able to engage in psychotherapy. (2) Parameters are repeatedly exceeded. Then one can hold the last safe level, and after one week slightly lower the parameters to an absolute low of a systolic BP of 76, diastolic blood pressure of 52, pulse 52.

At higher doses of propranolol, above 400 mg per day, substitution of the longer acting form of the drug smooths out blood-level fluctuations and adds safety against arrhythmias if one or two doses are missed. For a patient receiving 400 mg of regular propranolol per day, this substitution would result in a daily dosage of 80 mg and 20 mg of regular propranolol q.i.d. At ultra-high doses, we give 160 mg or more of long-acting propranolol four or five times daily, and regular propranolol on the same schedule. Patients who usually report problems with nightmares have had fewer night problems at higher doses of propranolol. (Clonazepam is also effective in reducing nightmares [Braun, in preparation].)

Propranolol is given prn in doses of approximately 10% or less of the total daily dose, as frequently as Q2h, since its half life is three hours. It can be, and often is, given in conjunction with a short-acting benzodiazepine. Patients generally report a synergistic effect.

Depression is an occasional side effect that requires careful assessment, and can be an additional indication to stop administration of the drug. When depression is observed during the propranolol regimen, the physician must ask:

(1) Is the depression a direct side effect of propranolol?

(2) Or, has propranolol "slowed" the patient's thoughts to the point where s/he is recovering depressing memories – e.g., of repeated childhood rape?

All inpatients are trained to take their own blood pressure and pulse prior to discharge, and are asked to follow the same regimen as do those that start the medication as outpatients. Our experience indicates that the need for propranolol decreases when the patient goes home.

In our experience, the two clear failures and one possible failure of propranolol therapy due to depression occurred when daily doses were at 240 mg or less.

Propranolol can be given on an outpatient basis provided the patient has the ability to understand and follow the physician's instructions and has continued full understanding of informed consent. I generally prescribe at dosage level and rate about half that of the inpatient schedule.

The outpatient must be trustworthy in drug compliance, must learn how to take and record his or her blood pressure and pulse before every dose of propranolol, and must keep a daily written log of orthostatic blood pressure, pulse and psychological-state to discuss with the physician. The patient must understand that propranolol cannot be abruptly discontinued without advice from the physician.

REDUCTION OF PROPRANOLOL

Medication may need to be withdrawn when there is a significant risk to the patient because of non-cooperative alters who may overdose or abruptly discontinue the medication. The rapid discontinuation of propranolol would represent a risk to the patient because of its association with cardiac arrhythmias.

The reduction of propranolol is accomplished gradually under our protocol, depending on the medical circumstances and the ability to monitor the patient's responses. Reduction may need to be done in an inpatient setting when special circumstances (such as a respiratory problem) arise while the patient is taking propranolol. A patient whose severe rapid switching had greatly improved on 800 mg per day of propranolol developed a viral pneumonia which necessitated the discontinuation of this drug. Due to the increased switching and acting out behavior or unleashing by the decrease of propranolol, rapid daily increase of clonidine was successfully attempted with careful monitoring of cardiac status as the propranolol was being withdrawn.

Rapid dose reduction, but not drug cessation, may sometimes be required when a patient goes from inpatient to outpatient status, as in the case of a patient who became uncoordinated when she returned to her teaching job at her

inpatient dose of 800 mg per day as a less volatile system of alters took control in the school environment. Also, reductions may be required when the patient has a therapeutic breakthrough. A similar phenomenon may be seen with lithium when the acute manic phase passes: the dose required at the acute manic phase may become a toxic dose when the acute phase ends. Proprenalol and metoprolol has also been used in conjunction with clonidine to lower the required dose of both.

CLONIDINE

The MPD patient who has concomitant bronchial asthma generally can be given clonidine safely, whereas propranolol is contraindicated. Clonidine, an imidazoline compound, is an alpha$_2$-adrenoreceptor agonist that lowers availability of norepinephrine at the synapse. It also stimulates alpha$_2$-adrenoreceptors in the brain stem, causing a reduced outflow from the central and sympathetic nervous systems and decreased peripheral resistance, renal vascular resistance, blood pressure and heart rate, although decrease in heart rate is significantly less than that which occurs with propranolol. This is one reason to combine the two medications (see below).

Thus, unlike the beta-blocking agents such as propranolol, the alpha-agonist clonidine reduces the norepinephrine available at the synapse, thereby reducing neuronal firing, and has few contraindications. I have used it effectively in over twenty patients.

Overall, clonidine is slower in its onset of action and somewhat less effective than propranolol in slowing the switching process in MPD patients. Also, it has a significant sedating effect. Clonidine is a good choice, however, when the patient has a propranolol contraindication such as bronchial asthma or Raynaud's disease.

I have used clonidine and propranolol simultaneously in a few patients. The combined use appears to be indicated when a high norepinephrine level is encountered in blood or urine, i.e., high MHPG and/or catecholamine level. Also, clonidine can be added to the medication regimen in patients who have responded to propranolol, but whose pulse rate has fallen to, or below, parameter while blood pressure remained above parameter. One may reduce propranolol a bit and add clonidine. I frequently use clonidine in conjunction with alprazolam, for the same reasons propranolol is combined with alprazolam.

Informed patient consent must be obtained, as described above for the protocol for use of propranolol. Clonidine's FDA-approved use is primarily as an anti-hypertensive. However, when it is used with MPD patients at non-approved high doses, its use must be fully explained to and understood by the patient and carefully followed by the physician as described above for use of propranolol. Again, the patient should be warned against stopping the medication suddenly.

The patient is usually started on clonidine at the anti-hypertensive dose of 0.1 mg, and increased by 0.1 mg every second or third day. Formerly, I increased dose every five to seven days. However, one patient was increased by 0.1 mg every day, with good results. Care is taken not to overmedicate when using rapid increases, as there is a lag between dosing and effect. Because of clonidine's sedating effect, the evening dose is increased, going up to 0.2 mg, then to 0.3 mg after several more days. The morning dose stays at 0.1 mg to avoid excessive daytime sedation. A mid-day dose of 0.1 mg may be added after the evening dose has reached the 0.3 mg level.

The therapeutic (psychiatric) daily clonidine dose is 1.0 mg to 2.0 mg in most patients. A few patients have been taken to 3.0+ mg per day and one patient is currently taking 4.0 mg per day. In the latter patient, the extreme dose of clonidine maintains a blood level of 2.6 ng/ml in the middle of the range used to treat hypertension (0.5-3.4), indicating an extreme variation in the metabolism of this drug. Monitoring of blood levels can be very useful, especially at high doses.

Clonidine has minimal pulse-slowing effect, but orthostatic pulse as well as BP is taken and recorded before each dose of medication is given as a safety precaution. Parameters are used to monitor medications as described above. Several patients had to be removed from clonidine because of oversedation.

SUMMARY

For theoretical reasons, propranolol and clonidine were tried alone and in combination for the treatment of anciety, impulsivity, and switching in dissociative disorder patients, especially those with MPD. It was found in open trial studies that propranolol is a useful adjunct to psychotherapy in very anxious and/or rapidly switching dissociative disorder patients when used in our experimental protocol. It is used in quite high dosage and under close medical supervision. It is preferable to initiate its use on an inpatient basis, but it has been administered successfully, albeit much more slowly, on an outpatient basis. The long-acting form of propranolol seems to be of value when using higher doses. These drugs can complement benzodiazepines in these patients and their effect has been reported to be synergistic.

Clonidine is of value for the same indications, especially in patients who cannot take propranolol. It can be used in conjunction with propranolol if indicated.

It must be reasserted that the use of medication reported in this paper is experimental and represents the open trial experiences of the author. Physicians wishing to undertake this approach should do so with great caution, after studying the literature on the medication, obtaining informed consent and closely supervising the patient and his/her physiologic responses. ■

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EDITORIAL ADDENDUM:

Bennett G. Braun, M.D.'s article, "Unusual Medication Regimens in the Treatment of Dissociative Disorder Patients: Part I. Noradrenergic Agents," is an important contribution to the literature which must be placed in perspective. It describes several pioneering efforts to establish a rational pharmacologic basis for offering relief and comfort to dissociative disorder patients. In a field in which little is firmly established and clinicians are eager to help distressed patients, there is danger that appropriate reservations will be bypassed and that readers will embrace preliminary reports with uncritical enthusiasm or desperation. It must be emphasized that the regimens it discusses are highly experimental, and have been tested in an open and uncontrolled manner in a specialized inpatient setting with skilled and readily-available medical consultation and back-up. Their suitability for use in other settings and their general applicability remains to be assessed, and cannot be assumed to be established. Those who would seek to replicate such interventions must bear in mind that the applications described are experimental and not FDA approved. Genuine informed consent and medical assessment, clearance, and ongoing follow-up are essential, and consultation is advised before proceeding.