Neuropsychopharmacologic Rationale:

Outline of the Medication Regime Established to Address Specific Identified Electrophysiological Abnormalities Associated with Localized Neurological Dysfunctions Involved in the Production of Impulsive/Explosive Aggression

I. Dysfunctions within the **Limbic System**:

A) Excessive/aberrant **Amygdalar** reactivity results in explosive emotional dyscontrol and overwhelming emotional re-experiencing, as well as increased perception of and reaction to threat.

The excessive/aberrant amygdalar reactivity is most effectively addressed with oxcarbazepine at a dosage of 35-50 mg/kg/day, or attainment of a trough blood level of 30-35 mcg/ml.

B) Inadequate **Hippocampal** attentional capability results in attentional and memory deficits.

This may be addressed with a stimulant (methylphenidate 0.4-0.6 mg/kg 3x daily, or dextroamphetamine 0.2-0.3 mg/kg 3x daily, or equivalent in a long-acting formulation), but only after the amygdalar dysfunction has been stabilized as described above. This is due to the extensive interconnection between the Hippocampus and Amygdala, which results in an overflow of stimulation from Hippocampus to Amygdala, thus leading to increased explosiveness in an already unstable Amygdala.

II. Dysfunctions in the **Dorsal Anterior Cingulate Gyrus** and **Ventromedial Prefrontal region**, primarily the **Orbitofrontal** region:

A) These dysfunctions result in an inability to adequately control impulses and emotions, problems with concentration and planning, and impaired problem-solving and executive functioning. These dysfunctions may be addressed with the following pharmacological interventions:

1. Alpha (2)-adrenergic agonists. i.e., clonidine or guanfacine have been traditionally used for 25 years to decrease noradrenalin function from the locus coeruleus to the frontal region.
2. Amantadine HCl, an agonist of the D-4 (dopamine) receptor, and an antagonist of the NMDA-glutamate receptor, in the frontal lobe.

Refer to enclosed: "Rationale for the Use of Amantadine in the Treatment of Frontal Lobe Dysfunction"

Rationale for the Use of Amantadine in the Treatment of Frontal Lobe Dysfunction

Inadequate frontal lobe function is demonstrated clinically as deficient impulse control, poor concentration, problems with working memory, weakness in executive cognition, and/or emotional dyscontrol. This dysfunction can result from traumatic brain injury, toxic or anoxic insults, or genetic abnormalities. The above described deficiencies, often labeled as a Dysexecutive Syndrome, are resultant from inadequate dopaminergic (primarily D-4) receptor function in conjunction with related increase in NMDA glutamate receptor activity. This is either a result of a neurometabolic "cascade effect" that occurs secondary to injury or insult, or is due to a genetic aberrancy of expression in the D-4 receptor.

Traditionally, in psychiatry, this Dysexecutive Syndrome has been addressed with alpha-adrenergic agonists (clonidine or guanfacine) which, actually, decreases norepinephrine activity frontally by occupying receptor binding sites with an inactive compound. This is sort of like putting a governor on the accelerator to compensate for the problem of "bad brakes" (e.g.; inadequate dopamine) frontally. This treatment concept was introduced by Bob Hunt about 30 years ago and has been relatively successful.

Alternatively, and frequently more effectively, one can use amantadine HCl in a 100-600 mg total daily dosage. This dosage should be given in equally divided doses first thing in the morning and mid-afternoon
(approximately 6-8 hours apart due to its short half-life). Amantadine directly addresses the dopaminergic deficiency by agonistically increasing dopaminergic activity in the anterior cingulate gyrus, orbitofrontal and/or other affected
ventromedial prefrontal structures. This agonistic effect occurs primarily at the D-4 receptor sites with only minimal effect at D-1 and D-2 receptor sites. Amantadine HCl has an added beneficial effect as a moderate NMDA glutamate receptor antagonist. Since the above described clinical picture of deficient impulse control, poor concentration, problems with memory, and/or emotional dyscontrol are seen in a hyper-glutamatergic state; restoring the D-4 to NMDA glutamate balance is beneficial in positively impacting the Dysexecutive Syndrome.

If amantadine HCl is used, one needs to be aware of the following facts:

1. Maximum benefit is usually achieved in the range of 200-400 mg per day. Little further enefit is seen beyond this dosage range. Dosages exceeding 15-20 mg/kg/day should be avoided due to the possibility if DNA damage in brain cells and development of behavioral deficits that have been recently demonstrated at doses of 30-60 mg/kg/day, but were not evident in the 15mg/kg/day dosage range.
2. In approximately 25% of individuals, the beneficial effect is lost between 4-8 weeks. This is thought to be due to "receptor exhaustion". This problem, and the corrective intervention for it, was discovered during its use (as Symmetrel) in the treatment of Parkinson's. The corrective action is to suspend administration for 48 hours and then reinstitute it at the previously effective dose. If this phenomenon occurs, it will reoccur at the same intervals, thus requiring repeating this procedure at the same interval as it first occurred. In our experience, this is best managed by planning the suspension for the closest Sat. and Sun. after week 4, 5, 6, etc. (whichever was the time of effect loss).
3. If amantadine HCl alone does not provide sufficient benefit, then clonidine HCl can be added since they have no drug/drug interaction and its actions are at norepinephrine receptors.
4. If the patient has had (or currently has) tics, then Amantadine may, rarely, cause a reoccurrence or increase of tics due to its action at D-1 and D-2 receptors. If this occurs, then discontinuation is necessary, and the tics should resolve.

AMANTADINE REFERENCES

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