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PSYCHIATRIC / NEUROBIOLOGIC / PSYCHOPHARMACOLOGIC REFERRAL

Evaluation for potential medication use should begin with identification of symptom clusters or specific psychopathology. The following list identifies problems that may be responsive to medication intervention and can be used to trigger a comprehensive neuropsychiatric evaluation that may in turn be the foundation for beginning psychopharmacologic treatment.

Psychopathology in developmental disability may be seen as multifactorial and therefore inherently complex. In order to rationally approach psychiatric problems occurring in the context of a developmental disability, it is helpful to consider separately the several layers composing the problem. If there is a specific genetic or structural problem, such as agenesis or partial agenesis of the corpus callosum, psychopathology common to the specific condition should be considered first, always keeping in mind that we are trying to make sense of behaviors or symptom complexes that have appeared in a patient suffering a specific known condition. For example, persons with poor corpus callosal function may be expected experience difficulty interpreting communications that require rapid or complex decoding. Simply knowing this general difficulty with information processing allows for understanding why ACC patients may view social situations as threatening or attempt to avoid complex social interactions entirely. Since the dominant and nondominant hemispheres process different aspects of emotional function, it may also be expected that sudden or complex emotional reactions might present severe challenges to ACC patients. In practice this means that a vulnerability to emotional instability is present. So, vulnerability to cognitive misinterpretation is accompanied by vulnerability to emotional dysregulation, particularly when the individual is challenged by sudden new information or the need to respond rapidly to emotionally challenging situation. In the most general sense, the vulnerability of the ACC condition magnifies the responses to normally stressful cognitive or emotional situations. If one considers that major psychopathology is, in part, composed of activation of the individual's response to stress that is in turn superimposed on other genetic vulnerabilities, resulting in manifest textbook psychopathology, it is then understandable that ACC patients are vulnerable to a broad spectrum of psychopathology, but that the ACC patient may appear more sensitive or more emotionally reactive than a 'normal' person. In summary, the following list of common psychiatric problems should be applied within the context of compromised callosal transfer of cognitive and emotional information.

Anxiety / anxiety disorders:

General anxiety / nervousness, panic attacks, social fear or avoidance, obsessive or compulsive behaviors may exist together with developmental syndromes. Chronic stress from functional impairments may, in turn, itself create anxiety over poor or slowed performance or may magnify anxious symptoms in persons who are genetically predisposed to anxiety or worry. ACC patients

are often socially avoidant or phobic and may exhibit emotional withdrawal. In general, anxious reactions or chronic anxiety disorders are now treated primarily with antidepressants, with or without an accompanying benzodiazepine. Antidepressants may be administered over time with fear of tolerance or addiction, and may also contribute significantly to better resistance to stress and often to serve to sustain the individual's coping responses in the face of what would otherwise be overwhelming stressors. In the treatment of anxiety, serotonergic antidepressants are preferred, and often reduce anxiety markedly within a few days. Functional improvement continues over weeks to months. Antidepressant therapy should be considered for individuals whose functional performance is degraded by anxiety, as well as for prevention of acute anxious reactions, such as panic attacks. Benzodiazepines should be reserved for treatment of acute anxiety, for patients who respond incompletely or adversely to antidepressant treatment. Another class of medication, the beta-receptor blockers may be considered in cases of performance anxiety or in cases of anxiety that leads to impulsive or aggressive dyscontrol.

Depression:

Apathy, frequent low mood, crying, emotional withdrawal, diminished social or work performance, or lethargy may represent a depressive disorder. Chronic stress may also create depression, and as with anxiety disorders, genetic vulnerability may predispose to depression in developmental syndromes. Depression is probably the most common psychopathology in developmental syndromes and screening for depression should occur frequently in vulnerable individuals. Treatment of depression in developmental syndromes is no different that in 'normal' psychiatric populations, but slow titration of the initial dosing regimen is wise, since many individuals with developmental syndromes exhibit sensitivity to psychopharmacological agents. The newer serotonergic antidepressants are preferred over the older tricyclic agents, primarily for safety and tolerance issues. The dual acting serotonergic and noradrenergic agents are used for more severe or treatment resistant cases.

Bipolar mood disorders:

Mood or energy cycling may represent the presence of a bipolar affective disorder. Seasonal energy cycling may occur in many people, but particularly in those who are genetically predisposed to cycling affective disorders. Developmental syndromes presenting with a history of mood cycling or recurrent depression or who have family members with bipolar disorder should be presumed to be potentially bipolar. If the diagnosis of bipolar disorder is established in an ACC patient, it should be treated as the primary psychopathology, i.e., the mood disorder must be first well stabilized before addressing coexisting complaints. Treatment of bipolar disorder is complex and is discussed separately.

Insomnia:

Poor sleep onset, frequent awakening, early morning wakening, or circadian dysregulation may be seen in anxiety, depressive, or chronic stress disorders. Attention to sleep regulation is often key to treatment of behavioral problems. Routine use of benzodiazepine hypnotic agents should be avoided in ACC patients. Other avenues of intervention for insomnia should be considered, including melatonin, ramelteon (a nonaddictive melatonergic agent), antihistamines such as

diphenhydramine or hydroxyzine, use of morning light therapy, or behavioral interventions, beginning with education surrounding sleep hygiene. It should be remembered that insomnia is very frequently a symptoms of another underlying problem or psychiatric diagnosis, such as an anxiety, depressive, or bipolar disorder.

Aggression:

Resistiveness, assaultiveness, property destruction may represent maladaptive responses to functional impairment or be part of the symptoms of anxiety, depression, or psychosis. Aggression may respond to treatment of the underlying disorder or may be treated as an independent symptom with medications that target aggression specifically. Aggression is promoted by depletion of serotonin in situations of chronic stress, so serotonergic agents may sometimes correct aggressive dyscontrol. If serotonergic antidepressants are not effective or contraindicated, use of neuroleptic agents or beta-blockers may be considered. Alternative agents also include alpha-adrenergic agents, such as clonidine or guanfacine, or the use of lithium or other antimanic agents such as divalproex or carbamazepine. Severe cases may require the use of multiple antiaggressive agents in combination. A thorough search for the cases of aggressive dyscontrol should be conducted. Psychopharmacology is not a substitute for understanding complex triggers to aggressive behavior. Behavioral interventions should also be applied when indicated and feasible.

Psychosis:

Extreme emotional arousal, auditory or visual hallucinations, delusions, nonsense language, marked confusion, loss of insight, or sudden changes in behavior may represent symptoms of psychosis that may require prompt intervention with antipsychotic medication. Psychoses in development syndromes may result from genetic vulnerability to schizophrenia and present as superimposed schizophreniform symptoms. Psychosis in the ACC population, as in other discrete developmental syndromes, may also result from reaction to overwhelming stress, or may be associated with other comorbid psychiatric or neurological conditions, such as seizure disorders or from severe depression or mania. Treatment usually requires use of an antipsychotic agent along with medications for coexisting conditions, e.g., antidepressants, mood stabilizers, or alternative anticonvulsant agents. Psychotic episodes are also traumatizing and require that the patient be managed in a supportive environment with adequate attention to security. Suicidal feelings must be carefully monitored in psychotic as well as depressed patients since impulsive self-injurious behavior may emerge within the psychotic or severe depressive episode.

Seizure Disorders:

Confusion, loss of behavioral control, smoldering emotionality, fugue behavior, irritability, or depressive symptoms may complicate management of developmentally disabled patients with seizures. The anticonvulsant medications may help or hinder coexisting emotional or cognitive problems. Careful selection of the anticonvulsant regimen, considering each agent's potential for inducing adverse cognitive or emotional side effects, coupled with an eye to sensitive dosage adjustment is required to optimize clinical and behavioral stability. In addition to cognitive or behavioral toxicity, anticonvulsant agents may create problems in pregnancy and must be

considered carefully when used in fertile patients. Likewise, anticonvulsants may alter the efficacy of contraceptive agents. Some anticonvulsants may reduce thyroid function, creating iatrogenic depression, or subtly lower mood and motivation or impair cognitive function. Optimization of an anticonvulsant regimen is a complex undertaking, since primary consideration for control of the seizure disorder is required, together with the targeted psychopathology. Switches to equally efficacious anticonvulsant regimen without cognitive or other side effects problems is often very rewarding, yet too seldom attempted.

Older anticonvulsant agents such as phenobarbital and Dilantin / phenytoin may be associated with deleterious effects on cognition. Widely used agents such as Tegretol / carbamazepine and Depakote / divalproex may also impair cognition although less frequently. Newer agents such a Lamictal / lamotrigine, Keppra / levetiracetam, and Zonegran / zonisamide are less likely to degrade cognition. Lamictal is approved for prophylaxis of mood episodes in bipolar disorder and should be considered to be a depression mood stabilizer. Its mood stabilizing properties may be well suited to the affective instability often seen in ACC. Each anticonvulsant agent has its side effect profile; serious adverse reactions are infrequent but regular monitoring is required to detect and manage emergent problems.

Attention deficits:

Problems with selective and sustained attention may occur in developmental syndromes and may represent typical ADD / ADHD or may represent difficulties based in the specific deficits of the particular developmental syndrome. In ACC patients, only a few case reports inform the literature. Since performance deficits based in the ACC pathology are already present, treatment aimed at attention deficits must be considered as trial and error efforts, but should not be neglected. Since attention generation and control mechanisms are complex, all of the classical medications used for classical ADD, including stimulants, the noradrenalin promoting agent, atomoxetine, and most recently, an alpha-2-adrenergic agent, guanfacine, may be of help. Antidepressant agents may also be helpful for augmenting function, including attention and motivation, in developmental syndromes. Atypical alerting agents, such as modafinil, armodafinil, or selegiline may be useful for patients with ADD in the context of ACC, given that they support subcortical and cortical information processing and are also known to help in depressive, amotivational syndromes, and excessive daytime sleepiness. Ideally, trials of medications for attention deficit or intended for enhancement of cognitive performance should be combined with formal performance testing done in serial fashion or with structured feedback from parents, teachers, or others who can contribute to judging the efficacy of the medication. Scales that measure behavioral components of attention deficits are widely available.

Co-morbid developmental disorders:

Autism spectrum disorders, Down's syndrome, Tourette's syndrome, Fragile-X syndrome, Angelman syndrome, and many other discrete neurodevelopmental syndromes may present with psychopathology that may be ameliorated by psychopharmacologic interventions. Each case must be evaluated with an eye to discovering symptoms that may respond to medication. Targeted symptoms are then addressed as previously described.

Medication side effects:

Side effects to medication regimens are always potentially present and must be identified in order to optimize both efficacy and tolerability. Careful attention to dosing is most important. Medication side effects are sometimes subtle and constitute one of the most common issues encountered in psychopharmacologic treatment of developmental syndromes. Considering the medication classes in use with a particular patient may identify side effect problems.

The class of medication with the most common troublesome side effects is the neuroleptic or atypical antipsychotic agents. The older agents are called neuroleptics or 'conventional' antipsychotics; all block the dopamine-2 receptor, the receptor that carries the neuroleptic or antipsychotic activity. This action is also effective against manic arousal, so neuroleptics were used initially for severely disturbed patients to gain behavior control and to reduce the intensity of emotional arousal in schizophrenia and mania. Prior to the 1980's when the 'low dose' strategies were shown to be efficacious, patients were often overmedicated. The key to best use of neuroleptic agents is to find precisely the most useful dose while carefully avoiding overmedication. Side effects appear in all patients with overmedication and are seen as excessive sedation, diminished activity, or most commonly as 'motor' complications, termed 'extrapyramidal' side effects, for the pathway in the brain that is responsible for the side effect when blocked. Extrapyramidal symptoms, also termed EPSE, appear in several forms. The patient may suddenly experience muscle tightening in face, neck, or limbs; this reaction is termed acute dystonia, and is treated usually with anticholinergic agents that are rapidly effective. Care must be taken to avoid acute dystonia, particularly in sensitive patients. Muscle rigidity or tremor may also occur in longer-term treatment and should indicate that the neuroleptic dose is too high. A third form of extrapyramidal reaction is called akathesia, meaning restlessness; the patient appears to be unable to settle when sitting or unable to relax and may pace without relief of discomfort. More subtle manifestations include continual shifting position while sitting. Akathesia is sometimes controlled by dose reduction, but may also be so intractable that other agents must be substituted.

The newer or 'atypical' antipsychotic agents are easier to use, but can also easily be overused. All also include blocking action at the serotonin-2a receptor as well as other receptors, depending on the agent. All also block the dopamine-2 receptor, as seen in the older neuroleptics. The side effect profiles of the newer antipsychotics are quite different; extrapyramidal reactions are much less frequent, but weight gain is sometimes severe. Patients on the newer agents must be carefully monitored for weight gain and associated metabolic changes, particularly in those whose are predisposed to obesity or diabetes by genetic factors. Zyprexa / olanzapine and Seroquel / quetiapine are known to be associated in many patients with marked weight gain. Risperidal / risperidone is less offensive; Abilify / aripiprazole and Geodon / ziprasidone are least offensive. As wi the older agents, dosing is critical, and may make the difference between a very effective and well tolerated treatment and a poorly tolerated and side effect laden treatment. Other side effects to the atypical antipsychotics include sedation, motor retardation, dry mouth, and lowered blood pressure.

It is important to recognize that the newer atypical antipsychotic agents are now all approved for treatment of bipolar mania, and some are approved for treatment of depression, as well as for

schizophrenia, the original indication. This means that many patients are more frequently put on the newer agents for indications other than schizophrenia, often for off label problems such as aggression. Careful monitoring is required to safely use these agents, so patients and families need to be aware of problems such as weight gain, lethargy, or excessive sleeping, and report potential problems promptly.

In summary, a comprehensive approach to the complex problems seen in developmental syndromes, including disorders of the corpus callosum, should address the difficulty by attempting to first understand the symptoms as functional impairment within the context of the structural disorder, in this case, ACC. Specific target symptoms for intervention should be established and treated where possible. It is important not to stop with suppression of the target symptoms, but to attempt to understand the patient with the larger context of the other layers of potential etiology, such as the trauma of the experience of functional disability. Disorders of the corpus callosum may create unique internal turmoil and external stressors as well, such as disturbances of interpersonal relationships or relationships within the family, school, or community, creating a manifest psychiatric problem that may take any of the various forms described above. Learning difficulties are very common and must be seen as chronically stressful. The patient's genetic heritage or family genetic background should be investigated carefully since a patient's family may be prone to anxiety, depressive, attention deficit, or psychotic disorders. Knowledge of the family genetics may often effective guide the clinician to the genetic diagnosis or to medication interventions that have been previously effective for other family members. Behavioral pathology seen in developmental syndromes does not always fit neatly into the diagnostic manuals, such as the DSM-IV. Therefore, psychopharmacologic interventions should not be approached casually, but should be employed with consideration for the complexity of the psychopathology to be addressed.

Other issues may emerge within treatment. The length of the intended treatment should be considered and discussed at the beginning of a medication intervention. Each medication should be individually discussed with regard to both benefits and risks. Informed consent should be obtained from either the patient or the guardian. Polypharmacy, the combined use of similar medications form the same chemical class, should be avoided. If polypharmacy is utilized, it should be explained and justified within the case record. Timing and methods for discontinuation of medication should likewise be discussed and charted. Intermittent, as needed (prn), medication dosing should also be carefully defined as to the conditions for which the medication is administered, by whom, and the circumstances and results of 'as needed' dosing episodes recorded. Serum level monitoring is required for some anticonvulsants and for lithium; regular monitoring with appropriate charting insures safe practice.

This outline is intended to sketch general principles of psychopharmacologic management in developmental syndromes. Each case is unique, however, and must be approached individually. No matter how skilled or experienced a practitioner may be, it is wise to understand that responses to psychopharmacologic interventions may require several or even many attempts to optimize the medication regimen before success is obtained. With diligent persistence and a good working relationship with the patients and family, results from psychopharmacologic management may be very satisfying to both patient and physician.