IPAP Schizophrenia Algorithm Node Notes

This is designed to be used in conjunction with the flowchart version available at www.ipap.org/schiz.

1: Diagnosis of schizophrenia or schizoaffective disorder

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It is important to establish diagnosis before considering treatment with psychotropic drugs. For patients who present with psychotic features, the differential usually includes schizophrenia, schizoaffective disorder, and bipolar disorder but may also include substance-induced psychosis, psychosis NOS, various organic psychoses. Other types of psychoses must be considered as well. This algorithm addresses the treatment of those who meet DSM-IV and ICD10 criteria for schizophrenia and schizoaffective disorder. The application of these criteria in clinical practice may be difficult in some cases. The problem of distinguishing schizoaffective disorder from bipolar disorder may be even more challenging, at least for the first several episodes. There are genetic and biological overlap between all three disorders which accounts for some of the difficulty in categorizing patients as one or the other. From the point of view of this algorithm, patients with a predominantly schizophrenic and schizoaffective clinical presentation at the time of evaluation, and with no clear history of bipolar disorder, are recommended to receive the same type and dose of antipsychotic drug treatment (Evidence Level B). There may be differences with regard to mood drugs, as will be discussed elsewhere.

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2: Consider critical initial or emergent issues affecting management and choice of drugs (here and at each subsequent treatment node)

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It is a principle of this algorithm that the clinician should consider the issues noted above before making the critical decision about acute treatment, the prelude to long term treatment. These issues may inform or override the considerations that would guide treatment in an uncomplicated clinical situation. This might occur when first encountering a patient in an emergency room or emerge during the course of treatment. Each of the issues is dealt with in separate notes under Nodes A-H.

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A: major suicide risk

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Patients who are suicidal need to be treated in an environment where they will be safe from immediate self-harm and adequate pharmacotherapeutic treatment can be initiated (Jacobs et al. 2003). Patients who are suicidal should be considered for clozapine treatment (Evidence Level B). The InterSePT study (Meltzer et al. 2003) demonstrated that clozapine reduced the risk of suicide attempts or hospitalizations to prevent attempts by 25% over a two-year period, compared to olanzapine, in patients with schizophrenia or schizoaffective disorder who were at high risk for suicide by virtue of an attempt in the last three years prior to entry or hospitalization to prevent such an attempt. The trial was randomized, blinded, and had an independent suicide monitoring board. Addition of antidepressants or mood stabilizers as determined by a non-blinded clinician to both groups did not diminish the clozapine-advantage. The US FDA evaluated this evidence, along with other studies which support the same conclusion, and approved an indication for clozapine to reduce the risk of suicide in schizophrenia and schizoaffective disorder. The study design did not permit determination of whether olanzapine reduced the risk of suicide or whether frequent clinical contact, which was equal in both groups, had any benefit by itself or in interaction with drug treatment.

Appropriate suicidal patients for clozapine treatment would be those who have made serious suicide attempts on other medications, who would be likely to take clozapine according to general guidelines, and for whom clozapine is not contraindicated. There is no evidence about the relative advantage of clozapine for suicidal patients who have never been treated with any antipsychotic medication, e.g. first episode patients. It should be noted however, that completed suicide in schizophrenia is at its highest rate in the early years of the illness.

The titration schedule and dosage of clozapine to be used should be adjusted for individual tolerability. Dosage of clozapine for patients who were not persistently psychotic on other medications is lower than for those who have persistent psychosis on other medications. It is usually 150-300 mg/day in the former group and 300-500 mg/day, in those who are treatment resistant. Doses up to 900 mg/day are sometimes needed. Clozapine monotherapy should be used whenever possible. There is no evidence that the addition of antidepressants or mood stabilizers enhances the ability of clozapine to reduce the risk of suicide. Stopping clozapine after some period, even if the patient is no longer suicidal, is highly likely to lead to a return of the underlying risk for suicide.

In the InterSePT study, the benefits of clozapine over olanzapine were most evident after 3 months of treatment. It is likely that the same advantages would be found over other antipsychotic drugs. The risk of suicide should be balanced against the side effect profile of clozapine, including the risk of agranulocytosis. If clozapine is insufficient to diminish suicidality, the use of adjunctive ECT or possibly antidepressants should be considered.

If patients refuse clozapine or are unable to tolerate clozapine, there is no evidence to assist with the choice among other antipsychotic drugs. An atypical antipsychotic would be superior to a typical agent based on their greater tolerability, enhanced effect on depression, and possibly lower risk of non-compliance.

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B: catatonia or Neuroleptic Malignant Syndrome (NMS)

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The clinician must distinguish between catatonia and NMS. Catatonia is a syndrome which is rare in patients who otherwise meet criteria for schizophrenia. Catatonia is more often found in mania, depression or systemic disease. It is recognized by the presence of two or more motor signs such as waxy flexibility, bizarre postures, stupor, or excitement or immobility for 24 hours or longer. The first treatment consists of the administration of high doses of benzodiazepines (BZD) or barbiturates. An intravenous "challenge" of lorazepam (1 mg repeated in 5 minutes) or diazepam (5mg) should relieve the motor signs within 10-15 minutes. Such relief is often dramatic.

If catatonia is reduced, oral lorazepam or diazepam is recommended, but dosages need to be high, on the order of 4 to 16 mg lorazepam

daily. A trial of two to four days should relieve the syndrome fully.

In the instances (probably less than 20%), when BZD are not effective, ECT is the treatment of choice. The parameters of ECT are bi-temporal electrode placement and daily seizures for three to four days (Evidence Level B).

NMS (with assistance of Ronald Gurrera, M.D.)

Neuroleptic malignant syndrome (NMS) is characterized by increased muscle tone, increased plasma creatine kinase (CK) activity, hyperthermia, labile autonomic hyperactivity, and altered mental status. It is generally the result of an idiosyncratic reaction to treatment with a typical neuroleptic, e.g. haloperidol, but may occur with the low EPS drugs such as olanzapine. Extrapyramidal symptoms may be less prominent or severe during NMS associated with atypical, compared to older, typical antipsychotic medications. If NMS is diagnosed, management should include: 1) discontinuation of all antipsychotic medications; evaluation of fluid balance and hydrate accordingly; 3) addition of a BZD, e.g. 1-2 mg lorazepam IM or IV, if signs persist or worsen after steps 1 and 2; 4) if signs persist or worsen after step 3, consider adding bromocriptine or dantrolene. In choosing between these options, some experts have advocated reserving dantrolene for medically severe cases in which increased muscle tone is prominent, while preferring to use bromocriptine in severe cases with prominent mental status changes (Shalev et al, 1991). The dose of bromocriptine is usually 2.5-5 mg PO or per NG tube TID (not to exceed 30 mg/day total) (Caroff et al. 1998). The dose of dantrolene is 1 mg/kg IV QID. ECT may be helpful and even necessary to prevent death when the previous recommendations are insufficient.

The rationale invoked to support these choices is that dantrolene is a ryanodine receptor (skeletal muscle sarcoplasmic reticulum calcium channel) blocker, and bromocriptine is a dopamine agonist with central activity. However, one should be aware that both agents are potentially toxic, and that evidence supporting their use is controversial. Studies indicate that these agents have some benefit [Kellam, 1987, Rosenberg and Green, 1989], no benefit [White and Robbins, 2000], or an adverse impact [Rosebush et al, 1991] in acute NMS. The largest review to date [Sakkas et al, 1991] found inconsistent effects from dantrolene and bromocriptine, similar to previous reviews.

Antipsychotic drug treatment will be needed in most cases after the acute stage is over. An interval of 1-2 weeks before starting antipsychotic drug treatment is recommended. Treatment should be with a drug with minimal EPS, e.g. quetiapine or clozapine. The possibility of recurrence of NMS with resumption of treatment is considerable.

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C: severe agitation or violence

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Addressing issues of severe agitation, violence and refusal to take oral medication precedes institution of treatment for acute psychosis per se. A combination of haloperidol and lorazepam is the most common form of treatment and is better than either treatment alone. EPS are seen in less than 5% when given together (Battaglia et al, 1997; Garza-Trevino et al, 1989): an anticholinergic drug should not be given routinely. The most commonly used regimen is 2 to 5 mg of haloperidol combined in the same syringe with 2 mg of lorazepam, given intramuscularly every 0.5 to 1.0 hour, up to three doses (Hughes, 1999; Hymen, 1994). Consideration should be given to the use of IM olanzapine or ziprasidone because of their low EPS. Both open and controlled studies indicate these drugs are more tolerable than haloperidol alone (Lesem et al, 2001; Wright et al, 2001; Daniels et al. 2004), and have equal or possibly greater efficacy. However, when combined with lorazepam, the advantage of the new agents with regard to EPS may not be worth the additional cost. Further short and long term studies are needed to establish this point. Patients with a history of EPS, especially dystonic reactions, should be given one of the newer agents, preferentially.

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D: non-compliance

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Non-compliance and poor adherence are characteristic of a high proportion of patients with schizophrenia or schizoaffective disorder (Evidence Level A). This is a greater problem with typical than atypical drugs but it is common even in those treated with atypical agents. A long-acting injectable form of an antipsychotic is clearly indicated in situations where it is highly likely that patients are not taking medication as prescribed and would have subtherapeutic exposure (Evidence Level A). Although the published evidence for long-acting risperidone is modest, it is reasonable to expect it has the same advantages over typical neuroleptic drugs with regard to low EPS and cognition as the oral version of risperidone (Evidence Level C). A controlled study (Kane et al, 2003) evaluated 461 mildly ill (CGI average of 3), cooperative patients able to consent to participate in the 12 week study. 67% of the patients on long acting risperidone dropped out (15% during the oral risperidone run-in phase, and 52% more sometime after the first injection. The use of long-acting risperidone requires overlap with oral medication for at least 3 weeks until blood levels from the long-acting risperidone are adequate. This is a disadvantage compared to long acting injectable typical antipsychotic drugs but will not be a problem in hospitalized patients, those who are cooperative, or whose medication taking is supervised by family or others. It may make this form of risperidone difficult to use in those patients with severe symptomatology who are uncooperative and lack insight. A typical agent may be necessary, at least initially. If these are effective, switching to long acting risperidone might be a step towards compliance with an orally active atypical antipsychotic drug. (Evidence Level A). Ideally, the oral medication used during the first three weeks of treatment with long acting risperidone should be risperidone as well but other antipsychotic drugs can suffice (Evidence Level C). A disadvantage of long-acting risperidone is that it must be given every two weeks compared to monthly injections of haloperidol decanoate. Long-acting risperidone 25, 37.5 or 50 mg q 2 weeks should be equivalent to 4-6 mg/day of oral risperidone (Evidence Level B). The price of long-acting risperidone is much greater than that of haloperidol decanoate but is comparable to that of oral olanzapine. As non-compliance leads to greater rehospitalization, long-acting risperidone could be expected to be cost-effective by reducing the number of days in hospital over an extended period. Additional research on this useful addition to the armamentarium for treating a subset of patients with schizophrenia is needed to determine the extent to which it should displace long acting typical antipsychotic drugs as the first choice when a long acting drug is indicated.

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E: Depressive or Manic Symptoms

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Depressive symptoms

Depression in schizophrenia may be difficult to distinguish from negative symptoms. Lack of energy, motivation, anhedonia and flat affect are characteristic negative symptoms. Feelings of sadness, hopelessness, low self esteem, suicidality and vegetative symptoms, e.g. loss of appetite, sleep disturbances are indicative of depression. Patients with clinically significant depressive symptoms that do not clear during the course of treatment with an antipsychotic drug may be given a trial with an antidepressant drug, but the little evidence that there is regarding this approach suggests it is effective in only about 25 % of patients. Whitehead et al (2003) reviewed 11 small randomized controlled trials and concluded that the literature was overall of poor quality. "The proportion improved in the antidepressant group was 26% (95% CI 10-42%) higher than in the placebo group..." The results provide weak evidence for the effectiveness of antidepressants in those with schizophrenia and depression and could be explained by publication bias (Evidence Level A). Tricyclic antidepressants have been found to be useful for treating depressive symptoms which emerge after the resolution of psychotic symptoms(Evidence Level B). There are no controlled studies supporting the use of SSRIs in patients treated with atypical antipsychotic drugs who are experiencing so-called post-psychotic depression, though this is commonly done.

Manic symptoms:
Two controlled studies have found that the addition of valproate to antipsychotic treatment when acute manic-like behavior (excitation, increased motor activity, grandiosity) is prominent decreases the time to control of these behaviors. However, the difference between placebo and valproate is maximal at several weeks but appears to be trending toward disappearance after 5-6 weeks (Wassaf et al. 2000, 2001; Casey et al, 2003). The benefits of more rapid control are often quite important for safety of patients and staff and may justify the additional expense of the atypical agents. Studies to determine the safety of removing the valproic acid after this point are needed. Lithium has had mixed results in this acute situation (Levinson et al, 1999). ECT may be a valuable alternative in this subgroup of patients with schizophrenia.
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F: substance abuse

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Substance abuse -- i.e., recurrent substance use leading to occupational or social impairment, etc. -- may have different implications from substance dependence -- i.e., tolerance, withdrawal, frequent or high dose abuse, etc. (see DSM-IV). Patients who intermittently abuse substances may generally be treated within the basic algorithm. Patients who are actively substance dependent need treatment provided for their substance abuse as well as their schizophrenia with the treatment administered simultaneously and in an integrated fashion by the same treatment team, wherever possible. Substance abusing schizophrenic patients are 8-13 times more likely to be noncompliant (Fenton et al. 1997) and show poor results even when their medication is actually taken.

If the patient is actively dependent upon substances, detoxification is advised as part of the initial treatment of the psychosis. At least some of the patient's symptoms may be due to the direct physiological effects of the substance, and these may improve after detoxification. Antipsychotic drugs are useful to control violent or agitated behavior as noted above but this must be done so as to avoid toxic interactions with the particular substance(s) of abuse that are on board. Prescribed benzodiazepines are ideally avoided, except as part of alcohol and sedative detoxification.

A "Dual-Diagnosis" treatment approach is usually advised as the next step for these patients. In addition to medication for the primary psychosis, relapse-prevention counseling, 12 step programs, and/or cognitive-behavioral interventions are recommended. Patients may need structured living situations that emphasize abstinence and contain the necessary supervision.

Systems of care that integrate substance abuse rehabilitation and recovery with mental illness treatment and rehabilitation appear to be the ideal. After acute stabilization, patients should be engaged in an ongoing education process for both disorders, and there should be clear-cut policies on responses to problematic behaviors.

Careful assessment of covert substance abuse should be performed before altering pharmacological treatment in response to inadequate response or relapse. Patients with substance abuse should be offered specialized treatment including motivational interviewing, cognitive behavioral therapy and family intervention (Barraclough et al. 2001). While many or most patients may not desire to stop substance use, treatment can be guided by their level of motivation (Ziedonis et al. 1997). In cases in which comorbid substance use interferes with antipsychotic compliance, a depot antipsychotic should be administered.

Preliminary evidence has suggested that clozapine treatment is more effective in reducing substance use than typical antipsychotic drugs (Buckley et al, 1999; Drake et al. 2000). The relative potential benefit of other atypical agents for substance abusing patients, although advocated by some experts, remains to be established (Noordsy et al. 2001; Smelson et al. 2002; Collaborative Working Group on Clinical Trial Evaluations, 1998). A role for adjunctive agents, such as naltrexone and disulfiram has not been supported in schizophrenia patients, whereas some preliminary evidence supports the use of antidepressants in dysphoric substance abusing patients (Krystal et al. 1999; Siris et al. 1993).

Potential interactions between substances of abuse and antipsychotic medications must also be considered. Cigarette smoking substantially increases hepatic metabolism of many antipsychotic agents; for example, smoking cessation can result in large increases in serum clozapine concentrations (Goff and Baldessarini, 1993). While clozapine can attenuate the euphoric and pressor effects of cocaine, it may also increase cocaine blood levels and may place patients at risk for syncopal episodes (Farren et al. 2000).
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G: prodromal or first episode

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If the patient is in the prodromal phase of schizophrenia, or a first episode patient, special approaches to acute and long term treatment are needed. These are discussed in the article below.
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H: treatment-induced side-effects

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A prior history of side effects to a medication should be taken into account in the initial evaluation. For example, a history of neuroleptic

malignant syndrome after administration of a particular medication or failure to respond to a trial of adequate dose or duration would suggest avoiding those medications in the acute situation which this section is devoted to.
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3: MONOTHERAPY:4-6 week trial of an atypical (AMI, ARIP, OLANZ, QUET, RISP, or ZIP) or, if not available, a trial of HAL, CHLOR or other typical antipsychotic

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This node represents the recommended treatment for the majority of patients with schizophrenia or schizoaffective disorder, if they are compliant with oral medications, not suicidal, not violent, or not otherwise requiring special considerations. Two key treatment principles are emphasized: monotherapy with a single antipsychotic drug and choice of drug based on tolerability, efficacy, cost-effectiveness and cost.

Monotherapy is a core recommendation of this algorithm. We eschew the use of multiple antipsychotic drugs at the same time. Patients with schizophrenia or schizoaffective disorder should receive an adequate trial with whatever antipsychotic medication is chosen by the clinician and patient, without casual addition of a second antipsychotic drug for the duration of that trial, which can be terminated because of lack of efficacy or tolerability. (Evidence Level C). As discussed above, the evidence to support the use of a mood stabilizer or antidepressant during the initial stages of treatment is minimal so clinicians should be cautious in starting treatment with both an antipsychotic and one or both of these other types of drugs. They may be added on an empirical basis if the initial response to monotherapy with an antipsychotic is inadequate after giving it a try for as long as seems reasonable. Clinical judgement is required in these cases.

The recommendation of this algorithm is for one of the five atypical antipsychotic drugs listed above because of their greater EPS tolerability and lower risk of tardive dyskinesia and their ability to improve cognitive function, especially verbal fluency, long term memory, and attention (Woodward et al. in press). The latter effects translate into improved functional outcome (Green et al. 1999). Choice among the five first line drugs will be based upon a number of factors that are discussed in the essay on Choice of Medication. Relevant factors include metabolic side effects, sedation, and cost.

Typical antipsychotic drugs may be used when atypicals are not available because of lack of approval within an entire country, financial reasons, etc. In such cases, the lowest effective dose of a high potency agent such as haloperidol, e.g. 5 mg/day, should be used. It is rarely necessary to go to doses higher than 15 mg/day. Small doses of atypical agents should not be combined with usually adequate doses of a typical agent. There is no evidence to suggest this is efficacious. Rather, the typical agents may prevent the beneficial effects of atypical agents.

Criteria for an adequate trial
A trial of a single antipsychotic drug should generally last 4-6 weeks with at least 4 weeks on a dose of the medication that is within the therapeutic range. **A trial terminated for lack of tolerability before it meets these criteria is not considered an adequate trial.**
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4: Trial of adequate dose, duration, no intolerability?

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An inadequate trial is one in which the dosage or duration is insufficient. This may have happened because the prescriber may have been unaware of appropriate duration, doses or because the patient was non-compliant or unable to tolerate the medication. An inadequate trial may sometimes occur because of concomitant medications which interfere with the action of an antipsychotic. Thus, polypharmacy, particularly when it leads to dosages of any antipsychotic being subtherapeutic on its own, may be considered a cause of an inadequate trial. A failed trial is one in which the medication dose and duration were adequate and in which no concomitant medication might be expected to interfere with efficacy but clinical response in core outcome measures, particularly control of positive symptoms was inadequate and had plateaued. In some instances, it may be impossible to determine if a trial was inadequate or failed. In such cases, it is probably prudent to consider it a failed trial.
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5: Psychosis persists after adjusting dose?

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If a patient fails to complete an adequately dosed, 4-6 week trial due to intolerance, the clinician should select another antipsychotic from among the options recommended in this node and complete an adequate trial of the second antipsychotic. If the intolerance was due to EPS, than amisulpride, aripiprazole, quetiapine or ziprasidone might be considered because of their very low EPS proclivity. Intolerance due to sedation might lead to a trial with aripiprazole or ziprasidone because they are less sedative than drugs like olanzapine and quetiapine. Intolerance due to lipid elevations and weight gain might lead to a trial with amisulpride, aripiprazole, risperidone or ziprasidone. See Choice of Medication information for discussion of a second drug choice after failure to respond to the first atypical or typical antipsychotic drug.
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6: MONOTHERAPY:Second 4-6 week trial of second atypical if available, or second typical, if not

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There are no data which bear upon whether a second antipsychotic drug should be tried when an adequate trial of one of the first line atypical agents fails to adequately control positive symptoms. It has previously been reported that when one typical antipsychotic agent fails, it is unlikely that a longer trial of that agent or a second trial of another typical agent will be effective. It is unclear if the same principles hold for atypical antipsychotic drugs. A large trial in the US (the CATIE trial) is underway and will help to answer this question. Until then, one must rely on expert opinion. We recommend a second trial of one of the atypical antipsychotic drugs other than clozapine if patients have persistent psychotic symptoms before turning to clozapine. The choice of the second drug will depend upon the first drug and possible reasons other than efficacy which may have caused or contributed to the treatment failure. Thus, if the first drug was risperidone and the reason for failure was related to EPS or prolactin increases at the most effective dose, then a drug such as aripiprazole, quetiapine or ziprasidone which have very low EPS and no effect on prolactin secretion would be reasonable.

Augmentation of risperidone or olanzapine with ECT in patients with treatment resistant schizophrenia has not proven to be more than marginally valuable (Evidence Level C).

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7: Adequate trial? (see 4)

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If a patient fails to complete an adequately dosed, 4-6 week trial due to intolerance, the clinician should select another antipsychotic from among the options at this node and complete an adequate trial of that antipsychotic. If the intolerance was due to EPS, than amisulpride, aripiprazole, quetiapine or ziprasidone might be considered because of their very low EPS proclivity. Intolerance due to sedation might lead to a trial with aripiprazole or ziprasidone. Intolerance due to lipid elevations and weight gain might lead to a trial with amisulpride, aripiprazole, risperidone or ziprasidone. See Choice of Medication for further discussion of choice of a second drug choice after failure to respond to the first atypical or typical agent.

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8: Psychosis or mod-to-severe TD or tardive dystonia after adjusting dose?

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Approximately 30% of patients might be expected to have an unsatisfactory response to two trials of typical antipsychotic drugs when response is defined as persistence of moderate to severe delusions, hallucinations and disorganized thinking (Evidence Level B). The percentage who will have an unsatisfactory response to one typical and one atypical or to two atypicals has not been satisfactorily assessed as yet but is being addressed to some extent in a large US study of patients who have responded partially to antipsychotic drugs (the CATIE study). The results of that study will not be available for several years. However, clinicians should consider other dimensions of schizophrenia when deciding whether response has been adequate: e.g. suicidality, cognition, negative symptoms, aggression, etc (Evidence Level B). Patients should also be considered treatment resistant if they have persistent suicidal thoughts, aggressive behavior on a chronic basis, or severe negative symptoms despite the control of positive symptoms, which is often the case because these domains of schizophrenia are independent of positive symptoms (Evidence Level B). In the case of suicidality, there is good evidence, including one controlled comparative study (InterSePT) , and much supportive evidence, that clozapine is the drug of choice for patients with schizophrenia or schizoaffective disorder who are at high risk for suicide as indicated, for example, by a recent serious suicide attempt (Evidence Level A).

If patients have tardive dyskinesia or tardive dystonia, an atypical antipsychotic is indicated (Evidence Level B), particularly clozapine and quetiapine, which have the lowest potential to compromise the extrapyramidal system.

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9: Six month trial of CLOZ up to 900 mg/day

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At this time, the preponderance of clinical evidence suggests that treatment with clozapine is indicated for the patient with schizophrenia or schizoaffective disorder who has failed two trials with other antipsychotic drugs, regardless of class (Evidence Level A).

This indication was first established in the US Clozapine study (Kane et al. 1988) and has been confirmed by many, but not all, studies. Occasional reports of other drugs being equivalent to clozapine in this regard must be viewed with caution because they often do not include only treatment resistant patients-- e.g., undisclosed numbers of patients who are intolerant of other antipsychotic drugs.

More importantly, the studies which find other atypical antipsychotic drugs equal in efficacy to clozapine have often not raised the dose of clozapine to high enough levels, which usually averages 400-500 mg/day, but may be less. The dose of clozapine should go up to 900 mg/day if patients can tolerate it before determining that it has not been more effective than prior treatments. The dose of clozapine must be slowly raised to minimize hypotension and sedation. Most importantly, a trial at adequate doses should last at least 6 months as over 50% of clozapine responders do not respond until they have been treated for more than 1-2 months (Evidence Level C).

No other antipsychotic drug should be given concomitantly except during the titration period, if indicated to control symptoms (Evidence Level A). Agranulocytosis occurs in less than 1% of patients treated with clozapine and is rarely fatal (Evidence Level B).

Monitoring the white cell count should be done in according to the guidelines of specific countries. Rechallenge should not occur if a patient has had agranulocytosis (Evidence Level C). Fluctuating white cell counts are commonplace and should not be a reason for discontinuation of clozapine (Evidence Level C).

Trough levels of clozapine of greater than 350 ng/ml have been reported to be more effective. Clozapine is definitely underutilized in many parts of the world, except China, and should be recognized as a valuable drug for the patient with schizophrenia who is persistently psychotic despite treatment with other antipsychotic drugs.

What if the patient refuses clozapine, or was unable to tolerate it during a past trial? First, determine if the patient's refusal is based on incompetence to consent to the trial. It may be that the patient is unable to appreciate the potential benefits due to denial or lack of insight into the severity of their disease. Appropriate action to obtain guardianship may be indicated. If there was a past trial of clozapine, obtain full details of what happened. Perhaps the side effects that led to premature termination of the trial were not contraindications to a re-trial of clozapine. Now that other treatments have been tried and the patient remains treatment-resistant, it may be worth retrying clozapine with more cautious dosage escalation, avoidance of potential drug interactions, and aggressive management of the side effects. Seizures, sedation, and hypotension are side effects that might be dealt with more successfully on a second try.

If clozapine is definitely not an option, and the monotherapy trials to this point have been fully adequate, there are a number of augmentation strategies to employ with non-clozapine antipsychotics. All have a very limited evidence-base for usefulness. (Evidence Level C) Detailed discussion of these may be found in other areas of this web site. If there are prominent comorbid symptoms along with the primary psychosis, these might be the target for adjunctive treatments. The use of mood stabilizers and antidepressants has been reviewed in the Emergent Issue 2B area. Other considerations could be antianxiety agents for anxiety symptoms; d-cycloserine, glycine,

or SSRIs for negative symptoms; cognitive enhancers for cognitive impairment, omega-3 fatty acids as a general augmentation; and (in our opinion vastly overused and least favored) combining two non-clozapine antipsychotics. (Freudenreich and Goff, 2002)
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10: Persistent positive symptoms despite clozapine treatment

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Clozapine-resistant schizophrenia (CRS)

Patients with treatment resistant schizophrenia who do not respond adequately to clozapine monotherapy are defined as clozapine-resistant schizophrenia (Williams et al., 2002) (CRS) or are called incomplete responders or superrefractory patients (Buckley et al., 2001).

The estimate prevalence of this subpopulation is 30% of the patients with treatment resistant schizophrenia. Since the prevalence of Antipsychotic TRS is 30-40%, it is expected that CRS patients represent around 10% of the total of patients with schizophrenia. Before establishing the diagnosis of CRS it is necessary to confirm that: 1) the patient is taking clozapine adequately for at least for 6 months; 2) clozapine blood levels are in the therapeutic range (350-450 g/L) and that uncontrolled co-morbid drug abuse is absent. As noted above, the most useful adjunctive treatment for these patients may be ECT. There is one report of the usefulness of pimozide augmentation but this needs to be replicated. Mood Stabilizers (Lithium, Valproate) may be helpful in some patients (Evidence Level C).

A small number of open clinical trials and case reports have suggested that the addition of a typical or an atypical antipsychotic drug to clozapine-treated patient who have persistent positive symptoms may be effective in some patients. However, a recent placebo-controlled trial demonstrated no benefit from the addition of risperidone to such patients (Yacioglu et al. Journal of Clinical Psychiatry, In press). It is recommended that the dose of clozapine should be increased to the highest level that patients can tolerate without excessive side-effects. It may also be useful to measure plasma clozapine levels to be sure that the trough levels are at least 350 ng/ml. The most robust evidence for improving positive symptoms in clozapine partial-responders suggests that a course of ECT is most effective. Maintenance of ECT may be necessary to maintain the advantage.
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11: Optimize CLOZ and/or augment with ECT or adjuvant medication, alternate strategies

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About 30% of patients with treatment resistant schizophrenia treated with clozapine will have persistent moderate to severe positive symptoms even after six months of treatment (Evidence Level B). Before deciding that clozapine is ineffective, one should be sure that the blood level is above 350-400 ng/ml (Evidence Level B). One may also raise the dose to 900 mg/day if it is tolerated (Evidence Level C).

Maintenance treatment with clozapine requires attention to dosage, side effects, compliance and using augmentation treatment judiciously and only when needed. There have been no systematic studies of the ability to reduce the dose of clozapine at some time after the optimal dose has been established. For that reason, if dosage reduction is attempted, it should be done very gradually (Evidence Level C). Dosage reduction may be needed to control the weight gain associated with clozapine in some but not all patients. Education about weight, diet and exercise are recommended from the beginning of clozapine treatment. Reducing or reversing the weight gain requires attention to diet and exercise as the first line of treatment.

Clozapine may be augmented with antidepressants or mood stabilizers in order to enhance its antidepressant or mood stabilizing properties (Evidence Level C). The timing of the addition of these agents needs to be determined by good clinical judgment because symptoms of depression, mood instability, and aggression will respond to clozapine monotherapy in many cases (Evidence Level C).

Of great importance in using clozapine is the possibility of withdrawal psychosis if it is withdrawn abruptly (Evidence Level B). This may be severe and unresponsive to medications other than clozapine. Therefore, whenever possible, clozapine should be tapered as another antipsychotic drug is introduced. One month of overlap is likely to minimize the risk of withdrawal psychosis. If clozapine is stopped for more than 48 hours, it must be restarted with a dose of 12.5 to 25 mg and then if there are no respiratory/cardiovascular symptoms, the dose may be quickly raised back to its previous level (Evidence Level C). If necessary to obtain some degree of relief of very severe psychosis after withdrawal, the initial doses may be higher

Attempts to augment clozapine with other antipsychotic drugs, be they typical or atypical, have generally been disappointing but the number of controlled studies is minimal. Open trials have sometimes reported beneficial effects of augmentation with risperidone. However, a recent double blind controlled study of adjunctive treatment with risperidone of schizophrenic patients partially responsive to clozapine has demonstrated the failure of risperidone to be effective for augmentation with clozapine. (Yacioglu EA et al, Journal of Clinical Psychiatry, In Press)

There has been interest in lamotrigine as an augmentation for clozapine, due to its glutamate antagonist properties. In addition to case reports, there is now a small double-blind, placebo-controlled crossover study involving the addition of 200 mg/day of lamotrigine (gradually over 8 weeks). (Tiihonen et al. 2003) There was a fairly small but statistically significant effect on positive symptoms, but no effect on negative symptoms. The study was not supported by any pharmaceutical firm. Replication and extension of these results would be of great interest.

Some experts recommend augmentation with amisulpride, pimozide, or sulpiride (Evidence Level B). Other experts recommend augmentation with ECT on the basis of a number of open studies and clinical experience with the combination (Evidence Level B). When it is effective, it is usually necessary to use maintenance ECT to prolong the benefit.

Alternate strategies: olanzapine and melperone for treatment resistant schizophrenia:
There is some anecdotal evidence that olanzapine may be effective in some treatment resistant patients when it is given in doses of 30-60 mg/day, significantly greater than the dose usually used for the bulk of patients with schizophrenia, 15-25 mg/day (Evidence Level C). The one published controlled study of high dose olanzapine compared 50 mg of olanzapine with 450 mg of clozapine. This small (N=13) trial found a good effect size for clozapine (>0.5) right in line with what other clozapine studies in this population have found, but there

was absolutely no benefit in the high-dose olanzapine arm. Also, almost half of the patients dropped out during the olanzapine treatment and none while on clozapine. Earlier studies had found that doses of olanzapine up to 25 mg/day were not more effective than typical neuroleptic drugs to improve positive symptoms in patients with treatment resistant schizophrenia (Evidence Level A) (A larger study of high dose olanzapine has recently been completed but has not been published.)

Melperone, a butyrophenone, available in some parts of the world is an atypical antipsychotic drug which has been shown to have some efficacy for treatment resistant patients with schizophrenia (Meltzer et al. 2001; Sumiyoshi et al. 2002). The dose effective in treatment resistant patients is significantly higher than that in non-treatment resistant patient. Doses of 200 mg/day are usually adequate in the typical patient with schizophrenia while doses up to 400 mg/day may be needed in treatment-resistant patients.
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12: Enter maintenance phase

updated November 02, 2004

Pharmacotherapy and Psychosocial Treatments
Maintenance treatment should continue with the medication which has been utilized and found to be effective and tolerable up to this point in following the algorithm. Atypical antipsychotic drugs are preferred for maintenance treatment because of their greater efficacy for cognition, mood and suicidality, and tolerability, leading to less risk of relapse. However, metabolic side effects will be important issues to follow closely, especially with olanzapine and clozapine (Evidence Level A). Both of these drugs produce the largest weight gain and increase the risk for the metabolic syndrome However, even with these two drugs, not all patients are affected, and there may be very good reasons to prefer these two agents. The metabolic syndrome and the effects of the atypicals to increase the risk for its development are discussed under Side Effects.

Key issues need to be addressed during this phase: dose, duration of medication, psychosocial treatments and parameters of follow-up and monitoring.

In most cases, the dose of an antipsychotic that was effective in treating the patient in the acute phase should be maintained at the same level during the first few months of maintenance treatment. However, lower doses may be possible during maintenance, particularly if dose-related side effects are a problem. If signs of relapse emerge after the dose has been lowered, the antipsychotic should be returned to the previous, effective level.

Patients who have had more than one psychotic episode are likely to need maintenance treatment indefinitely. Relapse rates as high as 90-100% have been reported in most series of chronic patients who discontinue medication. First episode patients should usually receive medication for at least one year. Thereafter, medication may be slowly tapered.

A third issue is psychosocial treatment. During maintenance treatment, patients may be more amenable to psychosocial and cognitive rehabilitation programs. The ability of atypical antipsychotic drugs to improve cognition and negative symptoms may lead to a better response to these adjunctive treatments than had been the case with typical neuroleptic drugs

A meta-analysis based upon 12 controlled studies of cognitive rehabilitation in schizophrenia taking into account the effects of type of rehabilitation approach (rehearsal or strategy learning) and duration of training showed mean weighted effect size of 0.45, with a 95% confidence interval from 0.26 to 0.64. Duration of training did not influence effect size. Group and family therapy, day care programs, drop-in centers, activity groups and assisted work preparation programs may be useful during this phase.

The patient should receive ongoing psychiatric follow-up including monitoring for efficacy, mood, side-effects, co-morbid psychiatric illness, compliance and substance abuse with encouragement for the patient to receive general ongoing medical care. Ideally the psychiatric care setting can provide monitoring of blood pressure and weight.

The patient, and when appropriate the family, should be encouraged to call and follow-up as needed. Including the family and caregivers is typically salient. Communication with the primary care provider is important. Technical accuracy and semantic precision is not enough when dealing with a patient who may be cognitively impaired. Effectiveness of communication requires the ongoing attention of the clinician.
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