
NASMHPD MEDICAL DIRECTORS'
TECHNICAL REPORT ON
PSYCHIATRIC POLYPHARMACY

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A series of technical reports prepared by the:
National Association of State Mental Health Program Directors (NASMHPD)
Medical Directors Council and State Medicaid Directors
66 Canal Center Plaza, Suite 302
Alexandria, Virginia 22314
Phone: (703) 739-9333 Fax: (703) 548-9517

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Report Preparation

Background and Purpose

This report is the seventh in a continuing series of reports initiated by the Medical Directors Council of the National Association of State Mental Health Program Directors (NASMHPD). The purpose of these reports is to provide information and assistance to state mental health directors on emerging clinical and service system issues. The technical report topics are identified by the NASMHPD Medical Directors Council in conjunction with NASMHPD leadership. Reports in the series are developed by members of NASMHPD divisions, NASMHPD affiliates, and outside experts.

New pharmacological agents for the treatment of persons with psychiatric disorders have increased the options for medical treatment of this population. The diversity of medications now available, along with the increased safety of many of the new agents, has created new opportunities for the use of multiple medications for a single condition. This therapeutic opportunity, however, comes with limited data on the safety and efficacy of these medications used in combination. The subject of polypharmacy, or the use of multiple medications in a single patient, requires thoughtful examination of its acceptability as a mode of treatment for persons with psychiatric disorders.

The purpose of this report is to review the most recent information on the use of polypharmacy, to outline guidelines for the use of polypharmacy, and to make recommendations that decrease the inappropriate use of multiple psychiatric medications in patients with psychiatric illness. This report is directed to clinicians, public mental health commissioners, consumer affairs representatives, Medicaid directors, and policy makers to help evaluate the use of polypharmacy in psychiatric populations.

Preparation of Report

This report was prepared from proceedings of a meeting held May 3-4, 2001, in New Orleans, Louisiana. Meeting participants included representatives from NASMHPD, state departments of mental health, and mental health consumer organizations. A facilitator directed the discussion to guide the creation of a document and a technical writer was present during the meeting to record the proceedings. A list of participants and their affiliations is included in Appendix 1. The views expressed by the participants are their own and do not necessarily reflect the views of the organizations they represent.

Prior to the meeting, participants reviewed literature pertaining to polypharmacy in psychiatry (Appendix 2). The materials provided background information to help ground the discussion in a shared context and guide the group's deliberations. This report builds on information presented in the literature and incorporates information related to the use of new psychiatric medications from meeting participants, reflecting their thoughts and experiences.

Editorial Review

A technical writer and an editor prepared the initial drafts of the report. Drafts were distributed for review and comment to all meeting participants and members of the NASMHPD Medical Directors Council's Editorial Board. The final report was reviewed, amended, and approved by the NASMHPD Medical Directors Council and does not necessarily reflect the viewpoint of the NASMHPD membership.

Problem Statement

Issue Definition

Polypharmacy refers to concurrent use of multiple medications in a single patient. Traditionally, polypharmacy has a negative connotation, implying an inappropriate or irrational use of multiple medications. The use of multiple medications can sometimes be an effective clinical intervention, however. The degree of risk and benefit associated with polypharmacy varies depending on the medications used and the characteristics of the patient.

In the published literature “polypharmacy” is used to refer to very different situations across different articles. Since common usage of the term is very imprecise, in assessing any study or opinion on polypharmacy it is important to be specific when interpreting the context of the situation. Unless otherwise specified, 'polypharmacy' in the text of this report will refer broadly to the use of two or more psychiatric medications in the same patient. For the purpose of this report, polypharmacy has also been divided into the following five categories that describe the impact and appropriateness of polypharmacy in greater detail:

- 1) **Same-Class Polypharmacy:** The use of more than one medication from the same medication class (e.g. two selective serotonin reuptake inhibitors, such as fluoxetine plus paroxetine).
- 2) **Multi-Class Polypharmacy:** The use of full therapeutic doses of more than one medication from different medication classes for the same symptom cluster (e.g. the use of lithium along with an atypical antipsychotic, such as fluoxetine plus olanzapine for treatment of mania).
- 3) **Adjunctive Polypharmacy:** The use of one medication to treat the side effects or secondary symptoms of another medication from a different medication class (e.g. the use of trazadone along with bupropion for insomnia).
- 4) **Augmentation:** The use of one medication at a lower than normal dose along with another medication from a different medication class at its full therapeutic dose, for the same symptom cluster (e.g. the addition of a low dose of haloperidol in a patient with a partial response to risperidone) or the addition of a medication that would not be used alone for the same symptom cluster (e.g. the addition of lithium in a person with major depression who is currently taking an antidepressant).
- 5) **Total Polypharmacy:** The total count of medications used in a patient, or total drug load. Consideration of total polypharmacy should include prescription medications, over-the-counter medications, alternative medical therapies, and elicited pharmacological agents.

Defining polypharmacy as occurring in one of the above categories only partially addresses the complexities inherent in polypharmacy. For one, medications are arbitrarily grouped into medication classes, which do not always reflect their degree of pharmacological similarity. When

class refers to target symptom cluster, such as “antidepressant” or “mood stabilizer”, it encompasses medications with very dissimilar mechanisms of action. When class refers to mechanism of action, such as “tricyclic antidepressant” or “SSRI”, the medications encompassed are very similar. In this paper, drug class refers to mechanism of action. In addition, some medications taken alone have effects on multiple neurotransmitters. The atypical antipsychotics, for instance, block the action of several neurotransmitters in the brain, and have been referred to as 'polypharmacy-in-a-pill' due to their complex mechanism of action. A recent trend of having single medications approved for multiple indications adds a further degree of complexity.

Polypharmacy has several negative consequences inherently associated with it.

- *The use of multiple medications increases the risk for medication-related adverse events and drug interactions.* For example, the concurrent use of the antipsychotic medications risperidone and clozapine has been observed to increase the amount of clozapine in the patient's body, potentially increasing the risk of adverse events associated with clozapine.
- *The use of multiple medications creates a more complicated drug regimen for the patient, potentially making compliance more difficult.* Similarly, it has been demonstrated that patients who perceive they are taking too many medications are less likely to comply with their drug regimen.
- *Multiple medications may confound the effects of one another.* In a patient taking multiple medications, a prescriber may not be able to distinguish which medications are helping, and which are causing problems for the patient.
- Where medications are used to treat the side effects of other medications, *polypharmacy potentially creates the need for more medication*, thus contributing to the problem.
- Finally, many new medications are expensive, and *the costs of the medication must be borne by the patient or another payer.* When the costs exceed the payer's ability or willingness to pay, the patient may be forced to choose which medications they receive.

There are clearly situations in which polypharmacy is appropriate or even necessary. The use of some medications in combination, such as the use of multiple mood stabilizers in a patient with bipolar disorder, is a common, accepted practice in psychiatric care. The use of multiple antipsychotic medications concurrently may be justified when providing acute treatment of symptoms during initiation of therapy with an atypical antipsychotic, during a cross-taper period where one medication is being replaced for another, or when all other therapeutic options for treating the patient with a single antipsychotic medication have failed.

Historical Framework

Medications for the treatment of severe mental illness became widely used in the 1960s after the introduction of the antipsychotic, chlorpromazine, and the mood stabilizer, lithium. By the early

1970s, same-class polypharmacy for schizophrenia using multiple antipsychotic agents was increasing in use, despite little clinical rationale. Research in the mid to late 70's clearly showed that same class polypharmacy with typical antipsychotics had no advantage over use of a single medication and caused additional problems. Subsequently, same-class polypharmacy has been considered inappropriate, particularly with antipsychotic medications. Provider education and drug utilization review procedures have historically focused on eliminating this practice.

In the 1980s, polypharmacy was rarely mentioned in the psychiatric medical literature, as the practice had subsided and the issue was less relevant. The introduction of new types of antipsychotic medications in the mid-1990s, as well as numerous other psychiatric medications, has made polypharmacy an issue again, since prescribers are able to experiment with combinations of the new agents. Now the issue has become more complicated. The medications are more advanced, new medication combinations have more clinical rationale to support them, and more combinations are possible. Case studies and anecdotal evidence point to situations where the use of polypharmacy has allowed patients who were previously unresponsive to a single medication to be successfully treated with multiple medications. Due to the lack of rigorous scientific evidence on the use of multiple psychiatric medications, however this issue needs to be further explored. Recommendations need to be developed to guide practitioners in assessing the appropriate use of combinations of psychiatric medications.

Current Prevalence

The use of multiple antipsychotic agents is a common practice. In Missouri, 25% of acute care patients and 33% of hospitalized patients are using more than one antipsychotic agent. Meeting participants agreed that the use of multiple psychiatric medications has been increasing steadily over the past decade.

Attempts to monitor and manage the inappropriate use of multiple antipsychotic agents appear to have been successful in some states. In Illinois, for example, a drug utilization review system has been established to minimize the use of multiple antipsychotic agents. Prescribers must receive approval for greater than 10 days of concurrent antipsychotic use. Long-term use of concurrent antipsychotic use in Illinois appears to be lower than that observed in several other states. Where multiple antipsychotics are being used, it often consists of the concurrent use of a depot typical antipsychotic medication with an oral atypical antipsychotic.

Scientific Evidence

There is very little research that examines the concurrent use of multiple antipsychotic medications. Those that do are generally either open-labeled trials or case studies. These studies typically investigate the effect of adding an atypical antipsychotic to clozapine, or the effect of adding a typical antipsychotic to an atypical antipsychotic. All studies have shown some positive effect; nonetheless, randomized, controlled clinical trials have not been conducted. In addition, most studies are short-term and involve predominantly white male patients. Variation in drug response or adverse reactions by sex or ethnicity cannot be adequately assessed. The long-term effects of polypharmacy remain largely unknown.

A recent study examined the medical records of 88 patients from 1983 to 1993 to determine indicators that predict mortality in schizophrenic patients. Investigators found that the maximum number of antipsychotic medications that patients took concurrently was a significant predictor of mortality. Indicators such as the average daily dose or total lifetime dose of antipsychotics failed to show statistical significance, suggesting that the difference in mortality was not due to disease severity alone. The authors attributed increased mortality to the cardiovascular effects of typical antipsychotic agents, as well as and the interaction between the medications and other medical conditions, such as asthma.

Literature that provides guidance on the use of multiple antipsychotics is almost entirely based on consensus statements or expert opinion. In general, such literature recommends that the combined use of typical antipsychotics is inappropriate, while combining atypical and typical agents or two atypical agents may be appropriate, under certain circumstances.

The primary reason a patient may receive more than one antipsychotic agent for an extended period of time is when a single medication is not effective. In order for this use to be justified, the patient first should receive adequate trials on several single antipsychotics. In reviewing past trials of antipsychotics, the dose and duration of therapy of single agents must be considered in order to evaluate the medication's effect. A medication does not reach a consistent concentration in the body until at least 5 half-lives after the initiation of therapy. The clinical effect of the medication may not be seen until weeks later. Therefore, a valid trial to determine the effectiveness of a psychiatric medication should allow at least 21 days of continuous use on the same dose for assessment of its response.

Circumstances in which multiple antipsychotic agents may be appropriate for temporary use are during medication changes and acute treatment. When medications are changed, there is a crossover period in which the dose of one medication is tapered down while another is tapered up. The old medications must be used concurrently with the new until the new medication takes effect. The prescriber must carefully avoid the 'crossover trap' where the patient shows clinical response before completion of the crossover and both medications are continued indefinitely. In acute situations, a typical antipsychotic may be used to provide immediate symptom resolution, while an atypical agent is initiated for long-term therapy. Care must be taken that acute use does not become chronic use through repetitive "as needed" and "one-time" use of the second agent.

More research exists regarding the use of multiple antidepressants for treatment of major depression. Since the 1970's, the efficacy of tricyclic antidepressants in combination with monoamine oxidase inhibitors has been well established. More recently, small studies have demonstrated the efficacy of tricyclic antidepressants in combination with selective serotonin reuptake inhibitors. There are also individual studies or case reports that report on other combinations of newer antidepressants, but they are not of sufficient power to support a broad conclusion of efficacy.

Support is stronger for the use of multi-class polypharmacy with mood stabilizers for the treatment of bipolar disorder. Research exists to support the efficacy of combinations of lithium and valproic acid, lithium and carbamazepine, and carbamazepine and valproic acid. In addition, there is sufficient support for the use of antipsychotic agents in combination with mood stabilizers for the

treatment of mania. Evidence is growing to support the effectiveness of topiramate and lamotrigine as part of a multi-class polypharmacy combination when used along with other mood stabilizers. However, evidence is also beginning to demonstrate that gabapentin will not prove effective as part of a multi-class polypharmacy regimen. The evidential lack of effectiveness of gabapentin in combination with other mood stabilizers is an important reminder to prescribers to remain skeptical of polypharmacy approaches until proven.

An examination of current treatment guidelines for schizophrenia, bipolar disorder, and depression reveals varied degrees of acceptance of polypharmacy in these psychiatric conditions. In schizophrenia, only one of three major guidelines includes polypharmacy as a part of the algorithm. The Texas Medication Algorithm Project (TMAP) guideline for schizophrenia includes the use of more than one antipsychotic agent in a patient at the sixth step of the algorithm, after the patient has failed as many as 5 steps of monotherapy. The American Psychiatric Association (APA) and the Expert Consensus Guidelines Series do not address antipsychotic polypharmacy as either a therapeutic option for schizophrenia or as a problem to be avoided. Both guidelines recommend augmentation polypharmacy with medication from other classes after several failed trials of single antipsychotics.

Both the TMAP and the APA guidelines for major depressive disorder recommend polypharmacy with different classes of antidepressants after several trials of different single antidepressants. The TMAP guidelines recommend using augmentation polypharmacy with non-antidepressant medication as early as the second step after using a single antidepressant and before using multiple antidepressants. The APA guidelines present either antidepressant polypharmacy or augmentation polypharmacy as being appropriate following multiple trials of a single antidepressant.

For bipolar disorder, the use of more than one mood stabilizer is considered appropriate early in the course of treatment. The TMAP algorithm for bipolar disorder recommends adding a second mood stabilizer in the second step of the treatment process. This is clearly a different message than we see with the antipsychotics, and is probably reflective of the relative safety of the mood stabilizer class of medications and the availability of a greater number of medications with different mechanisms of action.

Practice Issues

New pharmacological agents for the treatment of psychiatric conditions represent a significant advance from their predecessors. Medications introduced for schizophrenia, depression, and bipolar disorder in the past decade are at least as effective as the agents preceding them, and have been shown to have less adverse side effects on patients. The expanded selection of agents gives prescribers more alternatives from which to design a course of treatment for their patients. The safety profile of these agents allows for experimentation with medication combinations. While polypharmacy is often justified when a patient fails a series of trials on single medications, it is always necessary to remember these are potent agents. The concurrent use of any medications increases the risk for serious, unanticipated effects.

The availability of several new medications to treat severe psychiatric conditions challenges prescribers to reconcile the recovery principle of seeking more symptom improvement for their patients with the clinical principle of being pharmaceutically parsimonious. To facilitate balancing these concepts, prescribing must be focused on helping the patient as a whole, rather than on simply treating the patient's symptoms. Patient involvement in the assessment of risk and benefit when making medication decisions helps balance the desire for additional symptom resolution against the risks of increasing the patient's medication burden. Before starting a new medication, strong consideration should be given to reducing the number of medications a patient is currently taking.

The patient is the primary source for obtaining information to be used in a prescribing decision. Improving communication with the patient is likely to be the most effective way to eliminate the unnecessary or inappropriate use of polypharmacy. Involving the patient in the clinical assessment and treatment selection can improve the patient's compliance with, and self-monitoring of, their medication treatment.

A review of the patient's past medication use can identify previously successful and unsuccessful treatments and should include review of the rationale for each of the patient's current medications. A complete history of how the patient arrived at their current medication regimen provides the prescriber with an understanding of which medications are no longer working, which medications may be causing problems for the patient, or which medications are unlikely to work in the future. By reassessing the rationale for using each medication, and evaluating the effectiveness of each medication in relation to its intended purpose, the prescriber and consumer may be able to reduce polypharmacy.

For the patient, symptom reduction is not always the same as problem resolution. A patient may face transient problems that cause anxiety or depression and may need assistance working through their problems, rather than an increase in their medications. When they are successfully treated, patients with severe psychiatric illness may begin to grieve the losses they've experienced in life as a result of their condition. Patients may experience anxiety, worry, and depression due to lacking resources and support. Support may be needed to help them move through the grieving process. Effective communication can help the prescriber work with a patient to help resolve or work through problems, rather than to simply treat their problems with medications. Psychosocial treatment and support, such as assistance with housing, employment, and social support, may prove as essential to the patient's treatment as medication therapy.

To minimize maintaining the patient on unnecessary medications, the prescriber and patient should discuss the outcomes they expect from the addition of any medication. Patients are likely to base improvement on how they feel and how they function, whereas the physician may measure improvement as a change in target symptoms or the frequency with which the patient returns to the office. Clearly defined outcome will result in shared expectations. It will then be easier to assess the value of a medication in the future. A common vision of a reasonable outcome when therapy is initiated makes identifying an ineffective medication easier, decreasing the risk of polypharmacy.

Communication across health care systems can also improve the efficiency of a patient's medication regimen. With every change of setting or change of clinician, the patient risks starting a different set of medications. Different providers may have a different perspective on the patient's case and on the rationale for the patient's therapy. The better the patient's therapy is coordinated, the more consistent and rational the patient's medication therapy will be.

The use of polypharmacy is unlikely to diminish in the future. Many new psychiatric medications are currently in development, several of which may offer new approaches to treating psychiatric conditions. The current reimbursement structure for health care services generally does not provide incentives for improving communication across health care providers or for spending additional time with patients. Medication therapy is less expensive, easier to deliver, and easier to control than other forms of psychiatric treatment. Increasing clinician time with the patient, improving communicating across the health care system, and providing social support is more difficult to justify for reimbursement.

Special Populations

Children

Pharmacological treatment of children with psychiatric disorders is increasing, despite the limited availability of supporting evidence for its effectiveness. A recent policy statement from the American Academy of Child and Adolescent Psychiatry briefly addressed polypharmacy, stating "little data exist to support advantageous efficacy for drug combinations," and, "current clinical 'state-of-the-art' supports judicious use of combined medications, keeping such use to clearly justifiable clinical circumstances."

Only five psychiatric drugs—methylphenidate, dextroamphetamine, imipramine, sertraline, and fluvoxamine—are currently approved by the US Food and Drug Administration for use in children. All other usage of psychiatric medications in children is off-label. The costs of and obstacles to medication trials in children are great, and continue to limit research in this area.

Same-class polypharmacy is very rare, if not completely unused, in children. Multi-class polypharmacy and augmentation therapy are used, but data are not available to identify the prevalence. The May 1999 issue of the *Journal of the American Academy of Child and Adolescent Psychiatry* includes a series of articles providing an up-to-date review of the use of psychiatric medications in children. The only mention of polypharmacy in the series of articles refers to multi-class polypharmacy.

Despite the complexity of assessing and managing psychiatric conditions in children, external factors will likely continue to propel the growth of psychiatric medication use in children. A shortage of child psychiatrists has increased pressure to treat psychiatric conditions in children with medications. Managed care plans would rather deploy scarce resources toward medication treatment than consultation, which requires a greater amount of physician time and overall expense. Pediatricians and family practitioners are treating children in their practice, and have become more

comfortable with prescribing psychiatric medications to children. In addition, utilization review procedures reward the use of pharmacological treatments for psychiatric conditions.

Our culture continues to support, if not promote, the use of medications to alleviate problems. Factors such as school performance continue to drive the use of medication, as parents and teachers seek to improve educational outcomes for their children. Changing children's behavior with medication can obscure the need for families, schools, and communities to improve the environments in which children live. Greater research and guidance on the use of medications in children is needed to understand the implications of polypharmacy in this population.

Elderly

Special characteristics of this rapidly growing segment of the population increase their risk of problems related to polypharmacy. Multiple medical comorbidities in the elderly often lead to the use of multiple medications and treatment by multiple medical providers. Psychiatric conditions are often underrecognized and undertreated in elderly individuals and elderly patients who receive treatment are more likely to be treated with medications than with psychosocial intervention. Little research has been conducted which focuses on the use of medications in elderly persons.

Medical comorbidity is common elderly persons. The symptoms of disease and aging confound and complicate medication treatment. Health care providers are less able to distinguish the actual source of a patient's health problems. Medical comorbidities may render a patient more sensitive to the effects of medications and increase the likelihood of polypharmacy.

The treatment of multiple medical conditions often requires multiple medications. In elderly patients, the use of polypharmacy is the rule rather than the exception. Elderly persons currently include 13% of the population and consume 33% of the medications in the United States. Elderly patients in the community take an average of six medications, and elderly patients in nursing homes take an average of nine. Prescribing medications in the elderly is made more complex by changes in their ability to metabolize medications and variation in their response to medications. An elderly patient is more vulnerable to drug interactions and medication side effects than a middle-aged adult is. Greater baseline medication use in elderly patients makes medication interaction problems more difficult to avoid.

An elderly patient is often receiving treatment from multiple health care providers. Primary care providers are the most common source of psychiatric care services for this population. Health care providers will often be unaware of what other providers are prescribing unless the patient actually brings medications to their office visits for review. Without coordination of healthcare services, prescribing to this population occurs in the absence of fundamental information and without any means for a prescriber to anticipate medication problems.

Elderly patients receiving treatment for psychiatric conditions are much less likely to receive psychosocial intervention over pharmacological therapy. This occurs despite evidence that cognitive behavioral therapy works well with elderly patients. Although elderly patients are more likely to

receive medications than psychiatric treatment, when forced to choose among multiple medications, the elderly often choose not to receive their psychiatric medication.

Finally, there is a lack of research tailored to the use of medications in elderly patients. Pharmaceutical studies are typically restricted to participants 18 to 65 years of age. Despite limited research, there is emerging evidence of the effectiveness of psychiatric medications. Treatments for depression, psychosis, and Alzheimer's disease have proven to benefit this population. However, minimal research could be identified that focuses on the effects of using multiple psychiatric medications concurrently in elderly patients.

When using psychiatric medications in elderly patients, a few recommendations can be followed to minimize problems. Same-class polypharmacy is generally discouraged. The use of benzodiazepines, traditional antipsychotics, and tricyclic antidepressants should be restricted. Atypical antipsychotics and SSRIs are favored over typical antipsychotics and tricyclic antidepressants. The concurrent use of donepezil with an antidepressant or antipsychotic medication may be justified for providing cognitive enhancement along with treatment of behavioral problems in patients with Alzheimer's disease.

Consensus by Participants

The history of medicine includes many examples where limited knowledge has led to the widespread acceptance of practices that were later found to be inappropriate. The explosion of new medication therapies for the treatment of psychiatric illness since the late 1980's has resulted in a marked increase in the use of all types of polypharmacy. Psychiatrists and pharmacologists have not generated research and discussions throughout the field that was required to temporarily resolve the issue in the 1970's. As limited evidence is currently available to support the use of polypharmacy in psychiatry, this practice must be approached with caution. Currently, there is no evidence to justify same-class polypharmacy. There is growing evidence of a wide range of situations where multi-class polypharmacy, adjunctive polypharmacy, and augmentation are safe and effective treatments. In the face of this evidence, however, total polypharmacy is a growing concern. This section outlines practices that meeting participants felt were indicative of appropriate and inappropriate polypharmacy practices, and provides recommendations for health system changes that could be implemented to encourage the appropriate use of polypharmacy.

Recommendations for Patients and Prescribers

Meeting participants agreed that the following practices represent appropriate practice before, during, and after adding additional psychiatric medications to a patient's medication regimen:

- **Before adding a second medication to a patient**, the following are considered appropriate practice:
 - For most psychiatric disorders, at least 2-3 trials of monotherapy with chemically distinct classes of agents should be tried prior to treatment with multiple agents. Actual practice will vary by disorder. When polypharmacy is to be used, accepted evidence-based guidelines, if available, should be followed.
 - After failing therapy on single agents, the patient's psychiatric diagnosis should be reevaluated before initiating therapy with multiple medications.
 - Only one medication should be changed at a time. In order to assess the adverse effects of and therapeutic response to a medication, only one actual medication trial can be monitored and evaluated at any time.
 - The first thing a clinician should consider when a patient does not respond to a medication is whether the patient is taking the medication correctly, if at all. Therefore, consider the patient's current adherence to treatment before adding medications. To increase adherence, preference should be given to the simplest effective treatment regimen. Many psychiatric medications can be dosed once a day and very few need more than twice a day dosing.

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- o Before adding additional agents, a single medication should be given adequate time at an effective dose to produce a therapeutic response. This includes at least 5 half-lives at a single dose to reach a steady blood concentration, plus additional time to evaluate the clinical response and adverse effects of the medication. For antidepressants and anti-anxiety medications, several weeks are often needed to evaluate clinical response and adverse effects. For antipsychotics and mood stabilizers, several months may be required for response.
 - o An important aspect of polypharmacy is drug-drug interactions. A majority of psychotropic medications pharmacokinetic drug interactions are due to the Cytochrome P450 System (CYP450). Clinically significant drug interactions are involved in problematic drug side effects and ineffective pharmacotherapy. These interactions may be life threatening. Drug-drug interactions are understandable and preventable if a clinician has a comprehensive understanding of the liver enzyme system, CYP450. An excellent clinical reference is the APPI "Concise Guide to The Cytochrome P450 System: Drug Interaction Principles for Medical Practice" by Cozza and Armstrong, 2001.
 - o The prescriber and patient should define what they consider to be an acceptable response to the new medication and what type of response would result in discontinuation of the new medication.
 - o The patient should be educated on how long the medication will take to reach its maximum effect, and what kind of effects the new medication is expected to produce.
 - o The patient's functioning should be considered more important than treatment of the patient's symptoms. For example, the use of sedating medications may reduce some of the patient's symptoms, but may unfavorably reduce the patient's functioning.
 - o Consider treatment alternatives, such as the use of psychosocial interventions, before prescribing an additional medication.
 - o Before prescribing additional medication, the patient's total drug load should be addressed to consider the patient's ability to adhere to a more complicated medication regimen.
 - o The patient's ability to pay for or otherwise obtain their medications should be considered when adding to their therapy.
 - o Before adding an additional medication to a patient's total drug regimen, all other remedies the patient is currently taking should be addressed, including over-the-counter medication use, cultural remedies, herbal remedies, and illicit drug use.

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- o Before adding an additional medication to a complex patient, the frequency and duration of physician visits should be increased to allow for proper assessment of the patient's current medication regimen.
 - **During treatment with multiple medications**, these considerations should guide therapy:
 - o The principle of 'start low, go slow' should be followed when initiating new medications, particularly in elderly and pediatric patients.
 - o Drug interactions should be anticipated and monitored when an additional medication is added. If an interaction drug is added, blood levels of interacting medications should be checked where appropriate. For example, adding fluoxetine to clozapine has been associated with at least one reported death in the literature.
 - o The prescriber should communicate with all other health care providers involved with the patient.
 - o Interventions to improve adherence with and access to medication therapy need to be identified and implemented.
 - o For patients in an inpatient facility who have had their medication dose or regimen recently changed, time should be allowed for appropriate assessment of response before the patient is discharged or further medication changes are made.
 - o Bioethnic differences should be considered when assessing a patient's response to medications.
 - **After the patient has been using multiple medications**, the prescriber should consider the following points when monitoring ongoing therapy:
 - o Consideration should be given to discontinuing medications that do not yield the expected response.
 - o Cross-tapers initiated to switch the patient from one medication to another should be completed.
 - o Patients who are using multiple medications, and who are potentially suffering from medication-related problems, should be considered for a wash-out period as a part of reassessment. If possible, the medication regimen should be simplified by dropping psychiatric medications in order to reassess the patient close to baseline. This does not have to involve removing all of the patient's medications.

The following inappropriate use of polypharmacy should be avoided:

- In general, same-class polypharmacy should not be used to treat the same symptoms in a patient.
- More than one medication from any of the following medication classes should not be used in a single patient:
 - Typical antipsychotics (haloperidol, fluphenazine, etc.),
 - Selective serotonin reuptake inhibitors (paroxetine, fluoxetine, etc.),
 - Tricyclic antidepressants (amitriptyline, imipramine, etc.),
 - Monoamine oxidase inhibitors (phenelzine, tranylcypromine),
 - Stimulants (methylphenidate, amphetamine), or
 - Benzodiazepines (diazepam, alprazolam, etc.).
- More than two antipsychotic medications, typical or atypical, should not be used simultaneously.
- The dose of a medication should not be adjusted until the medication serum level has reached steady state and sufficient time to achieve therapeutic effect has passed.
- Patients should not be discharged from an inpatient facility without allowing adequate time for the effects of the medication to be assessed. Patients on polypharmacy at the time of discharge from a facility are at a higher risk of subsequent medication problems. An increased level of monitoring and support should be considered when the patient is discharged with a complicated medication regimen. This statement should not be construed as support for outpatient commitment.

Recommendations for Health Care Systems

A health care system that is capable of monitoring prescribing behavior and intervening when polypharmacy issues arise can minimize inappropriate use of polypharmacy. The following system considerations can improve the use of polypharmacy in the public mental health system:

- An information system should be available to monitor prescribing and be alert to polypharmacy issues.
- The use of accepted treatment guidelines should be encouraged.
- The standard of care for monitoring medication use should include electronic decision support systems that can monitor the inappropriate use of multiple medications concurrently and compare the use of medications with the patient's other medical conditions.
- One-time emergency medications and medications that are used 'as needed' should be evaluated as scheduled medications if they are used greater than three times a week for three of four weeks.
- A performance measurement system should be able to identify the prescribers who are most likely to prescribe multiple medications and intervene by peer review. Objective criterion should be developed to define inappropriate use and identify practitioner outliers.
- Use of pharmacy controls to reduce inappropriate polypharmacy presents an opportunity to improve the clinical quality of care while reducing rising pharmacy costs.
- Prior authorization mechanisms should restrict only the most inappropriate instances of polypharmacy. Immediate peer review should be available to allow for timely initiation of therapy.
- An electronic monitoring system should monitor disparities in prescribing practice among ethnic groups. For example, African-American patients are reported to receive more depot antipsychotics than white patients in some geographical areas, thus increasing their risk of adverse outcomes.
- Pharmacists need to accept responsibility in coordinating pharmacotherapy from multiple healthcare providers to ensure appropriate polypharmacy practices are followed.
- Physicians need to be made aware of the complexity of psychiatric medications and utilize the medication knowledge of pharmacists. Consumers should be educated to use one pharmacy for all of their medications.
- Drug Utilization Review processes in the public mental health system should be directed towards reducing the inappropriate use of polypharmacy.

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- At a minimum, psychiatric polypharmacy should not be used without the support of a psychiatric consultation. If the patient is from the geriatric or pediatric population, a geriatric or pediatric psychiatrist should be consulted, whenever possible.
 - All health care professionals who are involved in psychopharmacology should be encouraged to complete annual continuing education in this area.
 - Health care payers should design their reimbursement systems to better support psychiatric consultation. Increasing incentives for psychiatric providers to consult among members of a treatment team and to conduct a periodic and thorough review of a patient's case can help counter the increasing reliance on medication therapy.
 - Health care payers should support pharmacotherapy monitoring through reimbursement mechanisms, particularly in patients using complicated medication regimens.

Recommendations for Mental Health Research

Among the most significant findings of this report is recognition of the widespread prevalence of polypharmacy in psychiatry, despite the lack of research documenting its safety and effectiveness. Future research on psychiatric polypharmacy is unlikely to occur without modifying the current standard for clinical research. Randomized, controlled clinical trials (RCTs), the current standard for the evaluation of medications, are intended to compare single medications. They are designed to avoid any confounding that occurs with the use of additional agents. The National Institute of Mental Health and the pharmaceutical industry support this research design. If RCTs were designed to compare combination medication regimens, it would be mathematically impossible to study every potential medication combination. Alternative research designs must be used to collect more evidence of the outcomes associated with psychiatric polypharmacy. The availability of better information systems, better methodology, and large databases of patient outcome data allow for the design of naturalistic studies that identify practices associated with better outcomes. The development of standard performance measures for evaluating common polypharmacy practices can help establish benchmarks for comparing the prevalence of polypharmacy across public mental health hospitals. Such indicators of hospital performance can be related to hospital outcomes to approximate the impact of polypharmacy on the public mental health system.

Due to the complexity of treating patients with multiple psychiatric medications, and the health and legal implications of this practice, the NASMHPD Medical Directors Council recommends the following for future mental health research:

- The NASMHPD Research Institute should convene a panel of experts to develop indicators for appropriate polypharmacy practices. Applying these indicators to state psychiatric hospital data, benchmarks for polypharmacy in public hospitals can be established. These benchmarks can be used to evaluate hospital performance and contribute to future research on the prevalence of inappropriate psychiatric polypharmacy.
- Naturalistic trials, piggyback trials, and quasi-experimental research methods for evaluating the effects of polypharmacy should be accepted and employed as mechanisms for identifying the optimal medication combinations for use in the treatment of patients.
- Increased funding should be directed to standardized trials involving the addition of a second medication or placebo to a current medication in a group of patients who are not adequately responding to monotherapy.
- Research should be directed at identifying which patients are at the greatest risk for polypharmacy. This will allow for more directed interventions in the future.

Appendix 1: List of Meeting Participants

NASMHPD Medical Directors Council Technical Report Meeting on Polypharmacy

New Orleans, Louisiana
May 3-4, 2001

MEDICAL DIRECTORS COUNCIL

Michael Flaum, MD

Director
Iowa Consortium for Mental Health
University of Iowa College of Medicine
Psychiatry Research/MEB
500 Newton Road
Iowa City, IA 52242
Tel: 319-353-4340
Fax: 319-353-5439
michael-flaum@uiowa.edu

Steven J. Karp, DO

Medical Director
Office of Mental Health and Substance Abuse
Services
Pennsylvania Department of Public Welfare
502 Health and Welfare Building
P.O. Box 2675
Harrisburg, PA 17105-2675
Tel: 717-772-2351
Fax: 717-787-5394
skarp@state.pa.us

Joseph Parks, MD

Deputy Director for Psychiatry
Department of Mental Health
1706 East Elm Street
P.O. Box 687
Jefferson City, MO 65102
Tel: 573-751-2794
Fax: 573-751-7815
mzparkj@mail.dmh.state.mo.us

COMMISSIONERS

Mary Schumacher

Director
Behavioral Health Services Division
Department of Health
1190 St. Francis Drive, Rm. N3300
Santa Fe, NM 87502-6110
Tel: 505-827-2601
Fax: 505-827-0097
mschumac@health.state.nm.us

Leigh Steiner, PhD

Associate Director
Department of Human Services
Office of Mental Health
100 South Grand Avenue East
Harris II, 2nd Floor
Springfield, IL 62762
Tel: 217-782-3731
Fax: 217-782-2406
dhsmhyb@dhs.state.il.us

CHILDREN, YOUTH & FAMILIES DIVISION

Albert A. Zachik, MD

Assistant Director for Child & Adolescent
Services
Mental Hygiene Administration
Department of Health and Mental Hygiene
201 West Preston Street
Baltimore, MD 21201
Tel: 410-767-6649
Fax: 410-333-5402

Penny Knapp, MD

Medical Director
California Department of Mental Health
1600 9th St., Suite 150
Sacramento CA 95814
Tel: 916-654-2309
Fax: 916-654-3198
pknapp@dmhhq.state.ca.us

CONSUMER AFFAIRS**John Allen**

Office of Consumer Affairs
Mental Hygiene Administration
201 West Preston Street, 4th Floor
Baltimore, MD 21201
Tel: 410-767-1381
Fax: 410-333-5402
jallen@dhhm.state.md.us

Cindy Hopkins

Director
Office of Consumer Affairs
Department of Mental Health and Retardation
P.O. Box 12668
Austin, TX 78711-2668
Tel: 512-206-5759
Fax: 512-206-5770
cindy.hopkins@mhm.state.tx.us

OLDER PERSONS DIVISION**Stephen J. Bartels, MD**

Medical Director
Division of Behavioral Health & Developmental
Disabilities
Department of Health and Human Services
State Office Park South
105 Pleasant Street
Concord, NH 03301
Tel: 603-271-5747
Fax: 603-271-8704
Stephen.j.bartels@dartmouth.edu

NRI, Inc.**Robert Littrell, PharmD**

ORYX Project Director
NASMHPD Research Institute, Inc.
2357 Huguenard Drive, Suite 100
Lexington, KY 40503
Tel: 859-260-1960
Fax: 859-260-1682
littrell@pop.uky.edu

PHARMACY**Randy Malan, RPh**

Director
Pharmacy Services
Department of Human Services
222 South College Street, Rm. 107
Springfield, IL 62704
Tel: 217-785-8983
Fax: 217-785-9051
dhs9848@dhs.state.il.us

FACILITATOR**Bruce D. Emery, MSW**

Consultant/Mediator
Emery and Associates
709 Devonshire Road
Tacoma Park, MD 20912
Tel: 301-270-0530
Fax: 520-833-0807
emorybd@msn.com

TECHNICAL WRITER**Craig Roberts, PharmD, MPA**

Health Economics Fellow
Office of Health Policy and Clinical Outcomes
Thomas Jefferson University
1015 Walnut Street, Suite 115
Philadelphia, PA 19107
Tel: 215-955-4137
Fax: 215-923-7583
craig.roberts@mail.tju.edu

**NATIONAL ASSOCIATION OF STATE
MENTAL HEALTH PROGRAM
DIRECTORS**

66 Canal Center Plaza, Suite 302
Alexandria, VA 22314
Tel: 703-739-9333
Fax: 703-548-9517

Robert W. Glover, PhD, x29

Executive Director
bob.glover@nasmhpd.org

Roy E. Praschil, x20

Director of Operations
roy.praschil@nasmhpd.org

Appendix 2: Selected Bibliography

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