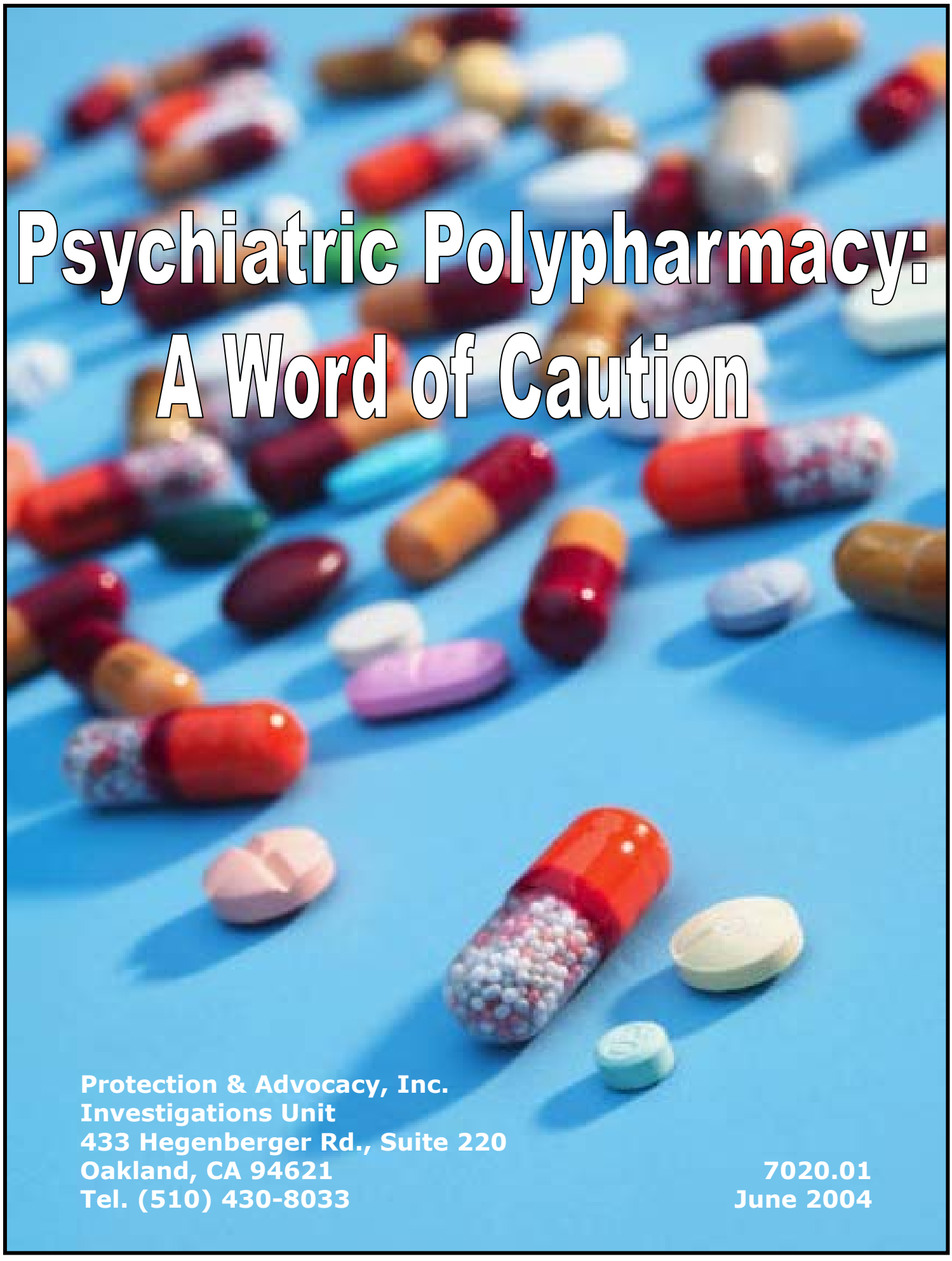

# Psychiatric Polypharmacy: A Word of Caution

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## Introduction

Protection & Advocacy, Inc. (PAI) is an independent, private, nonprofit agency that protects and advocates for the rights of persons with disabilities, including psychiatric disabilities. Under federal and state law, PAI has the authority to investigate incidents of abuse and neglect of persons with disabilities. 29 U.S.C. § 794e; 42 U.S.C. §§ 10801 and 15001 *et seq.*; Welf. & Inst. Code §§ 4900 *et seq.*

PAI has conducted several investigations into deaths related to the combined use of multiple psychiatric medications. Three recent cases were also reviewed by experts in clinical psychiatry, psychopharmacology and toxicology. In each case, the experts were critical of the polypharmacy regimen prescribed and the adequacy of the clinical response in the face of patient deterioration. In at least one case, PAI's experts concluded that the drug regimen was fatal. In the other two cases, polypharmacy likely contributed to the adverse outcome, based on the combined pharmacological effects of the medications used.

The medication regimen prescribed in each case was aggressive and unsupported by the patient's clinical presentation and the medical literature. As summarized by PAI's psychopharmacology expert, Dr. Charles Reynolds, "While it is true that a certain amount of polypharmacy in treatment resistant patients is considered a community standard, the polypharmacy demonstrated here is difficult to understand."

There appeared to be little clinical evaluation in the face of patient deterioration. Days lapsed between physician visits. Medication lists were not reviewed. Drug levels were not ordered, even when blood samples were available. Thorough medical work ups were not conducted. According to Dr. Reynolds, "The major problem existed in not recognizing the patient's medical state to be deteriorating and not consistent with the patient's diagnosis and thus not focusing on possible reasons for this deterioration."

PAI releases this report as part of its ongoing educational efforts to:

- Publicize the potentially fatal consequences of polypharmacy; and
- Encourage health care professionals and entities to implement safeguards when prescribing multiple medications in combination.

## Executive Summary

PAI recently investigated the deaths of three men associated with the use of multiple psychiatric medications in combination (polypharmacy). Each case was reviewed by three experts:

- Stephen E. Hall, M.D., a board-certified clinical psychiatrist,
- James Meeker, Ph.D., D.A.B.F.T., a toxicologist, and
- Charles A. Reynolds, Pharm.D., B.C.P.P., a psychopharmacologist

As the cases illustrate, a medication regimen which includes multiple psychiatric medications used in combination can be toxic and sometimes fatal, even when the prescribed doses of individual medications fall within the recommended ranges.

There are few scientific studies into the risks associated with using multiple psychiatric medications in combination. However, experts and researchers agree that the concurrent use of multiple psychiatric drugs increases the likelihood of unanticipated adverse effects, including death. According to PAI's clinical psychiatry expert, Dr. Stephen Hall, "The literature describes only certain specific drug interactions among antipsychotics and other psychotropics. However, these cases suggest that when multiple medications are used in high doses, cumulative effects may occur that can be dangerous for some patients."

If clinicians determine that polypharmacy may be warranted in an individual case, treatment and direct care staff must consider and carefully monitor the patient for potential toxic adverse drug interactions. According to PAI's psycho-pharmacology expert, Dr. Charles Reynolds, "Polypharmacy, like that seen in these cases, increases the likelihood of problems and places a special onus on the prescriber for more intense monitoring, especially when the patient begins to appear medically ill."

In the investigations of three deaths, PAI determined that the individuals were prescribed an excessive polypharmacy regimen which likely contributed to their deaths. Based upon its investigations, PAI recommends that clinicians:

- Thoroughly evaluate the patient, his or her symptoms and his or her medication regimen;
- Refrain from polypharmacy when they can; plan carefully and monitor the patient's response when they cannot;
- Only prescribe that for which there is a demonstrated need;
- Avoid using the same class of medication to treat the same symptoms;

- Consider drug interactions when prescribing multiple medications;
- Be familiar with how adverse drug reactions may manifest in the patient; and
- Carefully monitor the patient for potential adverse drug reactions, including cumulative anticholinergic effects[1] of psychiatric medication prescribed.

[1] Anticholinergic effects include dry mouth, blurred vision, difficulty urinating, decreased sweating, increased heart rate, and constipation.

## Background

Polypharmacy is broadly defined as the administration of more than one drug in a single patient. Polypharmacy occurs in most clinical settings, particularly those treating persons with chronic illnesses and the elderly (Kingsbury, Yi, and Simpson, 2001). Polypsychopharmacy is the practice of polypharmacy in psychiatric therapy and is the focus of this report. In this report, the term polypharmacy will be used for polypsychopharmacy.

The primary reason a person receives more than one medication is because clinical staff determines that administration of a single medication (monotherapy) is ineffective in adequately treating the individual's psychiatric symptoms (NASMHPD, 2001; Procyshyn, Kennedy, Tse, and Thompson, 2001; Rosack, 2000). Other reasons for prescribing more than one medication are to target specific symptoms, to treat two distinct but co-morbid illnesses in one patient, to address unremitting symptoms, and to treat extrapyramidal effects produced by a primary drug ("Evidence-based polypharmacy," 2003; Preskorn, 1995).

The use of multiple psychiatric agents is "common practice," according to a recent report by the National Association of State Mental Health Program Directors (NASMHPD) Medical Directors Council (NASMHPD, 2001). Studies report between 25-50% of patients (up to one-fourth of all outpatients and up to one-half of all inpatients) are prescribed more than one antipsychotic drug concurrently (Lelliott, et al., 2002; NASMHPD, 2001; Procyshyn, Kennedy, Tse, and Thompson, 2001). The prevalence of add-on or adjunctive pharmacotherapy[2] has been reported between 28-75% (Frye, et al., 2000).

Patient factors associated with polypharmacy include:

- a higher degree of disability (i.e., sicker patients);
- repeat hospitalizations within one year;
- younger age;
- being male;
- detention on an involuntary commitment; and
- a diagnosis of schizophrenia, bipolar disorder, or mania.

[2] Adjunctive polypharmacy is using one medication to treat side effects of another medication from a different medication class.

(Lelliott, et al., 2002; NASMHPD, 2001; Nichol, Stimmel, and Lange, 1995; Rosack, 2003; Tapp, et al., 2003). Ethnicity was not a statistically significant variable (Lelliott, et al., 2002).

There have been few randomized, controlled, scientific studies evaluating the effectiveness, risks and long term effects of using two psychiatric drugs in combination ("Evidence-based polypharmacy," 2003; Meltzer and Kostakoglu, 2000; NASMHPD, 2001; Preskorn, 1995; Rapp and Kaplan, 1981). Most drug studies involve using a medication in isolation and comparing it with either a placebo or a comparable agent (NASMHPD, 2001; Preskorn, 1995). The long-term effects of polypharmacy are largely unknown because most studies are short-term and fail to evaluate patients over extended periods of time (NASMHPD, 2001; Rapp and Kaplan, 1981). Combinations of more than two drugs is not supported with scientific research beyond the combined use of a mood stabilizer, an antipsychotic and an anti-anxiety agent (anxiolytic) to treat an acute manic episode in a patient with bipolar disorder[3] (Bowden and Wilcox, 2002; NASMHPD, 2001).

Experts and medical research consistently caution clinicians about the risks associated with polypharmacy. Each drug that is added to a patient's medication regimen raises the likelihood of an adverse outcome (Preskorn, 1995). Polypharmacy increases the risk of:

- adverse drug reactions and the severity of those reactions;
- drug-to-drug interactions;
- cumulative toxicity;
- medication errors;
- patient non-compliance;
- patient morbidity; and
- patient mortality.

("Evidence-based polypharmacy," 2003; Kingsbury, et al., 2001; NASMHPD, 2001; Werder and Preskorn, 2003)

[3] The use of two-drug combinations has been demonstrated in the treatment certain psychiatric disabilities, specifically bipolar disorder, intractable depression, schizoaffective disorder, and schizophrenia with a major depressive component (NASMHPD, 2001; Rapp, et al., 1981; Sernyak and Woods, 1993).

Researchers and clinicians repeatedly condemn certain psychiatric drug combinations and practices as irrational polypharmacy. These include the:

- Combined use of drugs from the same class to treat the same symptoms such as:
    - Typical antipsychotics (Fayek, Kingsbury, and Simpson, 2002; Kingsbury, et al., 2001; NASMHPD, 2001);
    - Benzodiazepines (Kingsbury, et al., 2001; NASMHPD, 2001);
    - Antidepressants from same drug family, including tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and monoamine oxidase inhibitors (MAOIs) (NASMHPD, 2001);
    - Stimulants (NASMHPD, 2001);
- Use of more than two antipsychotics, typical or atypical (NASMHPD, 2001);
- Change in the dose of a medication before the serum level has reached a steady state and sufficient time has lapsed for a therapeutic response (NASMHPD, 2001); and
- Failure to adequately evaluate and monitor patients prescribed a polypharmacy regimen.

## A. Mark Simmons

Mark Simmons was a 46 year-old male diagnosed with chronic undifferentiated schizophrenia. Some records also indicate Mr. Simmons was mildly mentally retarded. Since 1997, Mr. Simmons had lived successfully in the community, residing in board and care homes and participating in vocational programs. Mr. Simmons had occasional periods of decompensation and assaultiveness resulting in changes in his living arrangements and/or job placements. He had regular frequent contact with two consistent county caseworkers and an outpatient psychiatrist.

Beginning in 2001, Mr. Simmons had more frequent difficulties. This coincided with his parents' move out-of-state and his mother's diagnosis and treatment for cancer. Mr. Simmons was hospitalized on several occasions at local acute inpatient psychiatric programs and was prescribed multiple psychiatric medications in combination. In late February 2002, Mr. Simmons was voluntarily admitted by his county conservator to a 59 bed mental health rehabilitation center (MHRC) from an acute inpatient program. Mr. Simmons' attending physician at the MHRC, noting the aggressive polypharmacy regimen, wrote in his admission note, "[Mr. Simmons] currently on too many meds."

At the MHRC, Mr. Simmons was frequently "intrusive," "threatening," and "agitated." He appeared to be responding to internal stimuli. On several occasions, Mr. Simmons got into verbal altercations with peers and staff, inciting aggression in others. He also kicked or otherwise physically attacked male peers. Following these encounters, he was given additional doses of antipsychotic and/or anxiolytic (antianxiety) medication beyond that regularly prescribed (PRN) and was sent to his room for a timeout.

By early March, Mr. Simmons was taking standing doses of four antipsychotics, one antidepressant, one mood stabilizer, one anti-seizure medication, and one medication to reduce extrapyramidal side effects (EPS) along with daily PRN doses of another antipsychotic or an anxiolytic[4].

[4] Mr. Simmons was also prescribed Ditropan, 10 mgs twice a day for urinary incontinence and one iron tablet ($FeSo_4$), 325 mgs every day, which can cause constipation.

PAI's experts were critical of the prescription of multiple antipsychotic agents saying:

> While it is true that a certain amount of polypharmacy in treatment resistant patients is considered standard, the polypharmacy demonstrated here is difficult to understand. When past medication treatments were deemed ineffective, medications were added with questionable efficacy. The use of three antipsychotics all at the same time and at the doses used was redundant and raises a high index of suspicion.

PAI's experts were cautionary about the potential drug interactions, specifically additive anticholinergic effects[5]:

> I find a number of potential drug interactions with this medication regimen that could be contributory to the patient's presentation as well as his eventual demise. The ongoing prescription of Cogentin was unnecessary for this patient. Cogentin (benztropine) is one of a number of anticholinergic [medications] designed specifically to block the acetylcholine receptors. One of the actions is to prevent or reduce [EPS] associated with neuroleptics. Some neuroleptics themselves have significant anticholinergic effects. If a given patient is taking one of these neuroleptics, then adding a [medication] like Cogentin is unnecessary and might simply cause worse anticholinergic side effects.
>
> Here, there was no indication that Mr. Simmons had a significant EPS. He was on clozapine and other multiple [medications] with anticholinergic effects, including Ditropan for bed wetting; he was prescribed Haldol so somebody prescribed Cogentin for him, but the likelihood is that he didn't require it. It's disheartening that this series of psychiatrists just kept writing these orders without questioning, "Does he really need to be on Cogentin?"

In the days preceding his death, Mr. Simmons began showing signs of overmedication. He had an unsteady gait and several falls, including two resulting in head injuries. He was unable to stand up without weaving back and forth. He

[5] Anticholinergic effects include dry mouth, blurred vision, difficulty urinating, decreased sweating, increased heart rate, and constipation.

was increasingly confused and uncooperative. His pupils were sluggish and slow to react to light. He had low blood pressure (64/41) and a fast heart rate (120). The family expressed concern to MHRC staff that Mr. Simmons was on too many medications. Yet, there was no significant change in the medications prescribed. No blood work or cardiac evaluation was ordered.

After the second fall, he was sent to the local hospital for evaluation of his "change in mental status." A head CT scan was normal. Blood work included testing the Dilantin blood level although Dilantin had been discontinued the previous week. No other drug levels were evaluated. No electrocardiogram was performed. Upon his return several hours later, his speech was "less slurred, gait slow."

Clinicians at MHRC and the local hospital failed to evaluate if these changes were signs of overmedication. According to Dr. Hall:

> On March 18th, he had an episode of altered mental status. At 11:30 in the morning, he was sitting on a railing and he fell, striking the top of his head. [The staff at the MHRC] put him on closer observation. At 4:25 in the afternoon, he was found down in the bathroom. His speech was slurred. His pupils were sluggish. He was hypotensive. He was unable to stand up. It is likely that his drug levels were getting high. So they called 9-1-1 and sent him to the emergency room. They worked him up but they didn't get blood levels for any drugs except Dilantin. It would have been reasonable to see if he was overmedicated - to get levels of all of his medications at that point in time. Getting blood levels would not have been hard to do, especially while at the emergency room.
>
> On March 20th, [the MHRC physician] lowered two of his drugs by a trivial amount and didn't work him up any further. I would have lowered all of his medications more and eliminated one of the antipsychotics. I think if there is fault to be found, it is that they were not aggressive enough about managing his obvious physical deterioration.

At 7:00 a.m. on March 26, 2002, Mr. Simmons was found dead, in bed. He was cold to touch, not breathing and without pulses. He had last been seen alive at 1:00 a.m. Resuscitation efforts were not initiated because of obvious signs of death.

An autopsy was conducted by the county coroner. He listed the cause of death as, "polypharmacy overdose (quetiapine & clozapine)." A postmortem toxicology report[6] documented the following drug levels:

1. quetiapine 2400 nanog/mL [normal range 286 – 828 nanog/ml]
2. clozapine 2200 nanog/mL [normal range 40 – 340 nanog/ml]
3. norclozapine 1200 nanog/mL
4. gabapentin 17 mcg/mL
5. benztropine ~130 nanog/mL

PAI's experts endorsed the coroner's findings that Mr. Simmons' death was due to the combined effects of too much medication. While the blood levels for two of the medications were clearly in the toxic range, two others were above the upper limit of the recommended range. According to PAI's experts:

> Mr. Simmons appears to have been the victim of polypharmacy. He had significant levels of several different medications according to the coroner's report and these effects are additive…. The clozapine level was extremely high, as was the quetiapine level. Both of them were in the range that can cause death. But in addition, the gabapentin level was also extremely high. His gabapentin level was 17. Somebody on a typical regimen will produce a level much less than 17. It should be less than 8. Then he also had a Cogentin (benztropine) level of 130. The usual levels for someone who's getting therapy is 80 -120. It wouldn't have itself caused the fatality, but the anticholinergic effects of these various drugs are additive.

[6] Postmortem blood samples may not represent antemortem conditions. There is a build-up of medication in tissue, especially with people who have been on medication for a long time. After death, cells begin to break down. This releases the stored drug from the cells into the surrounding fluid. This release of medication may elevate the level of a drug postmortem above the level circulating when the individual was alive. Postmortem levels are a function of time lapsed between death and when the sample is taken, temperature of the stored body, location of where the blood sample is drawn, and the mechanism of blood sample drawn. Postmortem blood taken from the heart is known to have higher concentrations than blood taken from the periphery (J. Meeker, personal communication, November 2003).

> Furthermore, this patient was not properly monitored in relationship to the aggressiveness of the treatment regimen. Specifically, the lack of monitoring of blood levels, the relative acceptance of occasional hypotensive episodes without response and the inability to appreciate the drug interactions all contribute to his negative outcome.

## B. Sean Hartman

Sean Hartman was a 48 year-old male with a psychiatric disability who was living independently in his own apartment in the community and participating in outpatient treatment. He was diagnosed with bipolar affective disorder and/or schizoaffective disorder, bipolar type. His medication regimen included one antipsychotic, one mood stabilizer, and one anxiolytic[7].

On June 29, 2002, Mr. Hartman arrived at the emergency room of the county hospital accompanied by his sister. She had persuaded Mr. Hartman to voluntarily admit himself to the hospital because his condition had deteriorated significantly during the previous month. He had recently had a traumatic break-up with his long time girlfriend. Mr. Hartman was described by his treating psychiatrist as "grossly psychotic, grandiose, and delusional."

Hours after admission, he was placed in locked seclusion for aggressive behavior. He was in seclusion and occasionally restraints for most of his 10 day inpatient admission. During that time, he deteriorated despite aggressive polypharmacy. Mr. Hartman was prescribed two antipsychotics, two mood stabilizers, one anxiolytic, and one medication to reduce EPS. He also received daily several PRNs of an anxiolytic and an antipsychotic.

Despite the aggressive medication regimen, Mr. Hartman continued to exhibit psychotic and/or manic symptoms, delusional behavior, and poor impulse control. He became increasingly confused and unable to follow directions or care for himself. He frequently disrobed. His speech was rambling and incoherent. Over time, his gait became unsteady. His urinary and bowel output were diminished as he was too psychotic to eat or drink fluids. He lost nearly one pound a day, dropping from over 248 lbs. on admission to 239 lbs. the day before his death.

According to PAI's experts, Mr. Hartman likely had delirium with more than one cause. This may have included a confused state brought on by mania itself (manic

[7] Mr. Hartman was also prescribed one multivitamin tablet a day and Lotensin (for high blood pressure), 10 mg a day.

delirium) as well as delirium associated with excessive polypharmacy. According to Dr. Hall, "If given high enough doses of psychotropic medication, patients will become confused and appear delirious. This is a side effect which can be mistaken for psychosis. It can be mistaken for the illness that you are trying to treat in the first place."

The staff focused on Mr. Hartman's worsening psychosis rather than considering that there could be another cause to his deteriorating condition. More medication was added or doses were increased. As described by Dr. Hall:

> The problem with this case developed as the hospitalization continued. The patient goes from independent care and steady gait to total care and unsteady gait; from restraint for agitation and aggression to seclusion for confusion, safety, and inability to follow directions. The team here did not recognize that patient's medical state was deteriorating and was not consistent with the diagnosis. Rather than seeing the patient as getting medically worse, they focused on the worsening psychosis which appears closer to delirium.

Treating clinicians failed to aggressively and thoroughly evaluate Mr. Hartman. They appeared to not consider other possible causes of his symptoms. Other than checking his valproic acid and Topamax levels, blood levels of other medications prescribed were not evaluated. Although Mr. Hartman was eating and drinking little and had lost a considerable amount of weight, electrolytes were not elevated. There was no testing of creatine phosphokinase (CPK) levels or white blood cell count, possible indications of neuroleptic malignant syndrome, after initial admission blood work.

As summarized by PAI's experts:

> The treatment team could have done a better job of evaluating him. He was getting sicker. He was not urinating regularly. He was showing some urinary retention. He wasn't eating. He appeared delirious. Despite his deteriorating condition, the last physician orders were July 6th, six days before his death. If you've got a guy that's this sick and it's not exactly clear why, a doctor should have seen him every day and he didn't.
>
> On July 8th, [hospital staff] got a valproic acid level. While the condition of the patient worsened, no other labs were ordered after

> this. They should have gotten some other laboratory tests on him. They had the blood.

Experts were critical of apparent rote prescribing practices. Mr. Hartman's medication regimen included several drugs with anticholinergic effects. When he began showing anticholinergic symptoms, there was no comprehensive evaluation of the entire medication regimen (routine medications and PRNs), including cumulative anticholinergic effects.

According to Dr. Hall:

> He was on a bunch of anticholinergic medications including Ativan and Cogentin, and Benadryl with the Haldol PRN [injections]. He was showing signs of ill effects of anticholinergic medication and no signs of EPS. It would have been prudent to lower the dosages of Cogentin and Ativan. Between the two, he was getting a fair amount of anticholinergic medication.
>
> Physicians seem to forget about the cumulative effects of Cogentin, Benadryl, Thorazine - the anticholinergic drugs. There seems to be a trend for some physicians to forget about Cogentin when evaluating a patient's medication. [Cogentin] just stays on the [medication] list without any real strong rationale. In this case, it might have been the difference between dying or not.

On July 8th, one of the mood stabilizers (Topamax) was discontinued. On July 11th, one anxiolytic (Klonopin) was discontinued. But it was too little too late.

On the morning of July 12th, Mr. Hartman was found in the seclusion room not breathing and without a pulse. He was reportedly being monitored every 15 minutes. Resuscitation efforts were initiated but were unsuccessful. Mr. Hartman was pronounced dead at 11:00 a.m.

An autopsy was conducted by the county coroner. The coroner listed the cause of death as "probable adverse reaction associated with multiple drug therapy." While none of the medication levels upon autopsy exceeded the normal range, the combination proved fatal[8]. According to Dr. Hall:

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[8] A postmortem toxicology report documented the following drug levels:

1. olanzapine 0.023 mg/L [normal range 0.009 – 0.026 mg/L]
2. benztropine 0.009 mg/L [normal range 0.08 – 0.13 mg/L]

> The coroner basically found the cause of death was the effects of multiple drugs. The anticholinergic effect of these medications used in combination is a problem. The other is the total sedative load from Ativan, olanzapine and Depakote. His obesity and the multiple sedatives put him at risk for airway obstruction and respiratory compromise.
>
> This is a very sad case. This was a very young guy. He came to the hospital voluntarily. And he was dead less than two weeks later. It's not easy to say with certainty exactly why he died. But the coroner's conclusions make a lot of sense. It was a combination of his obesity and the anticholinergic medication load that did it.

## C. Daniel Quintero

Daniel Quintero was a 41 year-old male residing since early 2000 in a skilled nursing facility with a special treatment program. He was diagnosed with schizoaffective disorder, episodic alcohol abuse, and borderline intellectual functioning. He had gained over 100 lbs. in the last one and one-half years, going from 175 lbs. when admitted to 287 lbs. several days before his death. This weight gain was attributed to the psychiatric medication prescribed, specifically Seroquel and Clozaril.

Mr. Quintero also had a history of periodic falls. He fractured his right foot in the most recent fall in February 2001. These falls should have alerted clinicians to consider reducing his total medication load. In particular, PAI's experts questioned the use of Ativan, a medication known to make people unsteady on their feet.

For at least seven months preceding his death, Mr. Quintero took three antipsychotics, one mood stabilizer, one anxiolytic, one antidepressant, and one medication to reduce EPS. He also occasionally received an antipsychotic and/or anxiolytic PRN. On February 26, 2001, a consulting pharmacist notified Mr. Quintero's treating physician about concerns he had with the medication regimen, specifically the use of three neuroleptics (Seroquel, Clozaril, and Haldol) concurrently. The psychiatrist responded by describing Mr. Quintero as a

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3. lorazepam 0.015 mg/L [normal range 0.02 – 0.25 mg/L]
4. valproic acid 42 mg/L [normal range 50-100 mg/L]
5. haloperidol 0.008 mg/L [normal range 0.005 – 0.04 mg/L]

complicated case and claiming that he could not be managed on one antipsychotic medication.

According to PAI's experts, this explanation did not justify the ongoing prescription of three antipsychotics. Critical of the apparent failure to thoroughly evaluate the medication regimen, PAI's experts said:

> Although he was on three antipsychotics, at no point along the way did the physician take a look at him and say, "Is there any way we can change the medication regimen?" They just kept giving him the same medications. Keep in mind, the scientific literature does not support multiple antipsychotic use. If anything, two antipsychotics of differing types has the most support but only after prolonged adequate trials of single drug therapies have been shown to be ineffective, including a trial of clozapine by itself.

PAI's experts questioned the apparent failure of clinicians to consider the combined anticholinergic effect, saying:

> There is nothing in the record that showed any attempt to reduce the anticholinergic load. This was potentially a very problematic regimen because of all the anticholinergic drugs. The [Cogentin] was probably unnecessary while the patient was on Clozaril. The Cogentin was never reduced to see if he had EPS. In the side effect reviews that were routinely conducted by staff, they never mentioned extrapyramidal side effects.

On April 5, 2001, Mr. Quintero appeared to be sedated. His physician ordered staff to hold his medications. However, the records indicate Mr. Quintero received at least one dose of Ativan PRN following this order. Dr. Hall agreed that holding all medications was indicated on April 5th. Dr. Hall said:

> If the patient is falling asleep and seems to be overmedicated, you would hold the medicine. So [Mr. Quintero's physician] did that here. And then he received a 2 mg injection of Ativan. Yet there is nothing in the chart to suggest that he was agitated. On the contrary, he had been somnolent and that's why the doctor held the medication. It is speculative to say whether this played a role in his death. It's not an excessive dose for an agitated patient but if he was actually somnolent beforehand, it could have tipped him over the edge.

In the early morning hours on April 6th, Mr. Quintero received what appears to be a second PRN dose of Ativan. At 8:00 a.m., he was found dead in his bed. There were no witnesses to his collapse. The attending physician signed the death certificate, stating that Mr. Quintero had died from cardiovascular disease. The coroner declined to conduct an autopsy.

Mr. Quintero's family was not satisfied. They arranged for a private autopsy. Initially, the independent medical examiner determined that Mr. Quintero died from an overdose of Cogentin, with a benztropine level of 0.42 mg/L. In an addendum to his report, written after he had an opportunity to review Mr. Quintero's inpatient records, the medical examiner stated:

> [W]e are technically correct in attributing Mr. Quintero's death to a benztropine overdose, but it probably more accurate to attribute death to chronic, excessive polypharmacy in general…. The clinical history compels us to view this patient's predicament as a chronic state of toxicity. It is also possible that this degree of polypharmacy may have aggravated the patient's psychiatric symptoms, as a result of toxicity…. In summary, the cause of death is overmedication.

PAI's experts were not able to conclusively determine whether the drug regimen was the proximate cause of Mr. Quintero's death. However, they concluded that the prescribing practices fell significantly below the standard of care. Dr. Hall stated:

> One cannot say what the proximal cause of death was. Heart failure is a possibility. It could have been caused by the added weight or possibly the anticholinergic medication load. It seems most likely that Mr. Quintero died of a combination of anticholinergic medications. He was on three that have very strong anticholinergic side effects: Cogentin, Clozaril, and Benadryl[9]. They are synergistic – that is they are basically additive.

In conclusion, Dr. Hall said:

> For the eighteen months he was there, [Mr. Quintero] was just left on this regimen which was very aggressive. He was a sick guy. There was reason to treat him aggressively. But there was a distinct lack of initiative in evaluating this combination and attempting to reduce the

[9] While not prescribed Benadryl, high levels were found on autopsy.

total medication load. There is nothing in the record that suggested that a serious look was taken at the polypharmacy situation.

Fundamentally, the treating physician should periodically ask, "What medicines is he getting? Are they helping? Do they have the potential to hurt? Could they be making him worse? What can we do about it that is reasonable?" They never did that. There is minimal documentation in the chart by the psychiatrist. At no point along the way did they say, "Is there any way we can change the medication regimen because he is doing well?" or "He's doing poorly now and so we need to change his medication regimen." They just kept him on the same medication – even with symptoms of overmedication, the weight gain, the periodic falls, the lack of extrapyramidal symptoms. It was a poor medication regimen outside the standard of what is normally prescribed.

## A. Rationale for Polypharmacy

The primary reason a person receives more than one medication is because administration of a single medication (monotherapy) is ineffective in adequately treating the individual's psychiatric symptoms (NASMHPD, 2001; Procyshyn, et al., 2001; Rosack, 2000). Nearly 85% of physicians in one study reported prescribing more than one antipsychotic to patients who are refractory to monotherapy (Rosack, 2003). This includes the temporary use of multiple medications for acute treatment of psychiatric symptoms and the crossover period that may occur when changing medications (i.e., one medication is tapered down while the other is increased to a therapeutic level). Other reasons for prescribing more than one medication are to target specific symptoms, to treat two distinct but co-morbid illnesses in one patient, to address unremitting symptoms, and to treat extrapyramidal effects produced by a primary drug ("Evidence-based polypharmacy," 2003; Preskorn, 1995).

Some patients get caught in the "cross-over trap." Eighty percent of patients in one study switching from a typical to an atypical antipsychotic medication became "caught" (Tapp, et al., 2003). Although the intention was to completely switch the patient to the second medication, the patient's level of improvement while on both medications made the patient and/or physician unwilling to discontinue the first conventional medication (Tapp, et al., 2003). There is little scientific data to support the clinician or patient perceptions that combination antipsychotic therapy is more effective (Rosack, 2003). A cross-over period may be unnecessary when transitioning from one typical antipsychotic agent to another as researchers believe that the residual effects of the conventional neuroleptic lingers for a period after discontinuation (Meltzer, et al, 2000).

## B. Risks & Negative Consequences

The concurrent use of multiple medications increases the risk of serious, unanticipated adverse effects, including death (Kingsbury, et al., 2001; NASMHPD, 2001; Preskorn, 1995). The presence of one drug alters the nature, magnitude, and/or duration of the effect of another drug (Werder, et al., 2003). One drug may affect another drug's absorption, distribution within the body, or its metabolism or excretion thereby changing the blood levels of other drugs (Preskorn, 1995). Simply stated, the more medications prescribed, the more opportunities for drug interactions (Kramer, 2000).

For example, Risperdal and Paxil are known to increase the amount of Clozaril in a patient's body. This may increase the patient's risk of adverse effects from too much Clozaril (NASMHPD, 2001). Blood levels of certain antipsychotics may be affected by the concurrent use of anticonvulsants and some antidepressants (specifically SSRIs) ("Evidence-based polypharmacy," 2003). Dilantin lowers the levels of Paxil, Clozaril and Seroquel. Discontinuing Dilantin will raise the blood levels of these medications although the dose has not changed (C. Reynolds, personal communication, January 2004). Typical neuroleptics may reduce mood stabilization (Frye, et al., 2000). This is of particular importance when using antipsychotics in the treatment of persons with bipolar disorder.

The concurrent use of medications can amplify each individual drug's side effects. Two medications with very mild sedative effects can cause significant sedation when used in combination (Kramer, 2000). Similarly, drugs that cause mild weight gain may cause severe weight gain when used concurrently (Kramer, 2000). Using certain antipsychotic medications in combination with anticholinergic drugs may potentate the anticholinergic effects of both (S. Hall, personal communication, July 2003). This can cause a patient to become confused, dehydrated, constipated, and even develop a fatal cholinergic crisis[10].

The risk of drug toxicity or overmedication increases when using multiple medications at maximum prescription dosages. Research shows that sicker patients not only get multiple medications, they get them at higher doses (Rosack, 2003). One British study found that antipsychotic polypharmacy results in patients being prescribed higher doses of antipsychotic medication (Lelliott, et al., 2002).

The likelihood of death is directly proportionate to the number of medications a person with a psychiatric disability is taking, even when controlled for underlying diseases (NASMHPD, 2001; Werder, et al., 2003). One study found an increased risk of mortality in persons with schizophrenia with the use of more than one antipsychotic medication concurrently (Waddington, Youssef, and Kinsella, 1998). The design of this study permitted exclusion of deaths caused by suicide and other unnatural causes typically attributed to increased mortality in this population

[10] Patients prescribed more than one antipsychotic medication were more likely to receive an anticholinergic medication as compared to patients on monotherapy (Procyshyn, et al., 2001). In one study, 55.6% of patients discharged from the hospital on an antipsychotic polypharmacy regimen were prescribed an anticholinergic agent, as compared with 36.8% of patients discharged on a monotherapy medication regimen (Procyshyn, et al., 2001).

(Waddington, et al., 1998). Researchers attribute the increased mortality to the cardiovascular effects of many psychiatric medications and the interaction between these medications and other medical conditions, such as cardiac and respiratory conditions (NASMHPD, 2001). The author of the study concluded, "The greater the maximum number of antipsychotics given concurrently, the shorter was patient survival" (Waddington et al., 1998).

## A. Mr. Simmons, Hartman and Quintero were each prescribed an excessive polypharmacy regimen which likely contributed to their deaths.

PAI conducted an investigation into each of the cases described above. Each case was reviewed by three experts:

- Stephen E. Hall, M.D., a board-certified clinical psychiatrist,
- James Meeker, Ph.D., D.A.B.F.T., a toxicologist, and
- Charles A. Reynolds, Pharm.D., B.C.P.P., a psychopharmacologist.

In each case, the experts found fault with the polypharmacy regimen prescribed and the adequacy of the clinical response in the face of patient deterioration. In Mr. Simmons' case, the coroner and PAI's experts concluded that the polypharmacy regimen caused his death. In the other two cases, investigators were less certain about whether the drug regimen was the sole cause of the death but felt it was a contributing factor.

Mr. Simmons, Hartman and Quintero were on a considerable number of psychiatric medications, including two or more from the same drug class (antipsychotic medication) targeting psychosis. Medications were added with questionable efficacy. The medication regimen in each case included a prescription for Cogentin. Yet none of the men were demonstrating extrapyramidal side effects. Clinicians appeared to have failed to consider the cumulative anticholinergic effects despite the emergence of symptoms.

Dr. Hall said:

> Physicians forget about Cogentin when they are evaluating a patient's medications. It just stays on the medication list without any real strong rationale. This is prescribing by rote. Because [the patient] was on an antipsychotic, he was automatically prescribed Cogentin. It is illogical when somebody's already on a lot of other anticholinergic medications.

In each case described above, the patients showed signs of possible drug toxicity and/or additive anticholinergic effects in the days preceding their deaths. In the opinion of PAI's experts, clinicians did not thoroughly evaluate the patients despite sudden marked changes in their presentation and failed to act swiftly enough to address their symptoms. Dr. Reynolds commented, "These patients were not

adequately monitored in relationship to the aggressiveness of the treatment regimen."

Medication lists were not reviewed. Drug levels were not ordered, even when blood samples were available. Thorough medical work-ups were not completed, including evaluation of cardiac functioning and possible electrolyte and metabolic problems. Medication doses were not lowered quickly or by a sufficient amount. According to Dr. Hall, "If there is fault to be found, they were not aggressive enough about lowering medication doses and managing symptoms of overmedication."

There appeared to be little clinical evaluation in the face of patient deterioration. Days lapsed between physician visits. PAI's experts said:

> The major problem existed in not recognizing the patient's medical state to be deteriorating and not consistent with the patient's diagnosis and thus not focusing on possible reasons for this deterioration. There was a distinct lack of initiative in trying to think about how to treat [the patient]. I am a little perplexed that caring physicians did not hold medications while trying to diagnose what was going on.

## B. Polypharmacy increases the risk of serious adverse effects, including death.

Experts and medical research consistently caution clinicians about the risks associated with polypharmacy. Using multiple psychiatric medications in combination increases the risk of:

- adverse drug reactions and the severity of those reactions;
- drug-to-drug interactions;
- cumulative toxicity;
- medication errors;
- patient non-compliance;
- patient morbidity; and
- patient mortality.

The degree of risk posed by polypharmacy varies depending upon the medications prescribed and characteristics of the individual patient. However, each drug added increases the likelihood of an adverse outcome.

## A. Thoroughly evaluate patients, their symptoms and their medication regimen.

An individual's clinical presentation and diagnosis should be thoroughly evaluated before prescribing psychiatric medication and particularly when contemplating polypharmacy. Clinicians should review the patient's past medication use to identify which medication has previously been successful and which has been unsuccessful. In reviewing past trials, clinicians must consider the dose and duration of monotherapy to evaluate the medication's effect.

An individual must be given adequate trials of several single psychiatric medications of sufficient duration and dose to evaluate the medication's effects. NASMHPD considers a valid trial to be at least 21 days of continuous use on the same dose and recommends at least two to three trials of monotherapy with medication from different classes. Mood stabilizers and antipsychotics may require longer trial periods lasting several months. After failing to respond to several monotherapy trials, a patient's diagnosis should be reevaluated before initiating polypharmacy.

If a patient is not responding to a medication prescribed, before adding medications clinicians must evaluate whether patient compliance is a factor. Clinical staff should involve the patient in assessing his or her response to medication and selecting treatment options. This increases patient compliance and self-monitoring. A complicated medication regimen likely increases non-compliance.

## B. Refrain from polypharmacy when one can; plan carefully and monitor the patient's response when one cannot.

Monopharmacy is the goal. Therefore, clinicians are urged to attempt to treat the individual's psychiatric condition with one drug if possible. Before adding a new medication, clinicians must first consider reducing the number of medications an individual is taking. Physicians should review the rationale for each medication and clinical effectiveness in the patient's current regimen. Treatment staff should evaluate the patient's total drug regimen, including one-time doses, PRNs, over-the-counter medications, herbal remedies, and illegal drugs. NASMHPD considers one-time and PRN medications used more than three times in a week for three of four weeks part of a patient's scheduled medication regimen.

Clinicians should only change one medication at a time to more accurately assess the patient's response and presence of adverse effects. Changing several medications simultaneously makes it nearly impossible to determine which change is producing the clinical effect.

Physicians are urged to complete medication changes. The old medication should be discontinued once the new drug is at a therapeutic level for a sufficient period of time. Some medications do not require cross-titration. At times, a patient's clinical status during a medication change may discourage physicians from completing the titration. In the case of combination antipsychotic therapy, research does not support the clinician or patient perceptions that the combination is more effective than using one drug in isolation.

Clinicians should periodically monitor blood levels of medications prescribed, especially when the patient shows signs of possible toxicity or with medications likely to have drug interactions. As summarized by Dr. Reynolds, "Polypharmacy increases the likelihood of problems and places a special onus on the prescriber for more intense monitoring, especially when the patient begins to appear medically ill." Symptoms indicating a necessity for testing include sedation, gait changes, speech changes, increase in falls, constipation, urinary retention, and changes in mental status from baseline or diagnosis.

Facilities and programs providing pharmacy services are urged to implement mechanisms by which pharmacists and clinicians are notified of risky medication combinations. For example, clinicians may be notified when prescribing more than one medication from the same class or when using more than two antipsychotic medications simultaneously. Combinations of medications with cumulative anticholinergic effects should be considered risky and warrant advising the treating physician to monitor for potential problems. Prescribing physicians should take these notifications seriously and fully reevaluate the patient, the medication regimen and the patient's response to each medication prescribed. Peer review, pharmacy consultation and drug utilization review processes are further means to ensure appropriate polypharmacy practices and to reduce inappropriate polypharmacy use.

### C. Only prescribe that for which there is a demonstrated need.

Clinicians must review medication lists carefully with the goal of eliminating medications that have no clear benefit. Physicians should evaluate the rationale for prescribing each medication and its effectiveness in relation to its intended

purpose. Anything that is not necessary or does not serve a specific function should be eliminated. If a medication trial of sufficient duration shows little or no clinical response, its utility should be questioned. When the outcome from the trial does not yield the expected response or the response is not impressive, consideration should be given to discontinuing the medication.

Patients receiving combinations of psychotropic drugs are at risk because of the additive anticholinergic side effects these medications. Clinicians may prescribe by rote the prophylactic use of anticholinergics in patients receiving neuroleptics or ignore the total anticholinergic load a patient is receiving.

According to Dr. Hall:

> Mild anticholinergic side effects are dry mouth, mild constipation (which frequently patients will not mention), blurry vision, dry mucus membranes, delay in the ability to urinate. They can progress to more severe side effects. Typical anticholinergic toxicity is a worsening of the simple side effects – inability to urinate, inability to defecate, sleepiness or sedation, confusion, delirium, slurred speech, gait changes. It can be mistaken for the illness that you are trying to treat in the first place. The staff mistake anticholinergic toxicity for worsening psychosis and a need for even more medication.

**D. Avoid using the same class of medication to treat the same symptoms.**

According to NASMHPD, there is no evidence supporting same-class polypharmacy. The use of two drugs from the same group (antidepressant, neuroleptic, minor tranquilizer, etc.) can rarely, if ever, be justified. Research shows that same class polypharmacy with typical antipsychotic agents has no advantage over use of single medication and causes additional problems. Specifically, more than two antipsychotic medications, typical or atypical, should not be used simultaneously. The use of multiple antipsychotics for an extremely long period of time provides more risk than benefit.

**E. Consider drug interactions when prescribing multiple medications and carefully monitor the patient.**

When adding new medications to an existing drug regimen, possible adverse drug interactions should be anticipated and monitored. While there is little scientific research of specific drug interactions, based upon the known pharmacokinetics and

pharmacodynamics[11] of each medication, drug interactions are likely. In some cases, these interactions may be life threatening. Additive pharmacology and pharmacokinetic interactions that occur when medications are used in combination increases the likelihood of problems and places a special onus on the prescriber for more intense monitoring, especially when the patient begins to appear more ill.

[11] Pharmacokinetics is the study of the metabolism and action of drugs, particularly the absorption, duration of action, distribution of action, and method of excretion. Pharmacodynamics is the study of a drug's action on the body. (Thomas, 1993)

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Dr. Meeker has published 15 articles in scientific journals and has given over 40 scientific presentations at various meetings around the country. He is the current President of California Association of Toxicologists (CAT). Additionally, Dr. Meeker received the American Academy of Forensic Sciences 1991 Regional Award, was on the Journal of Analytical Editorial Advisory Board from 1992 to 1997, and had a voluntary appointment as a Clinical Assistant Professor with Stanford University from 1992 to 2002.

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