THE UNIVERSITY HOSPITAL
Pharmacy News
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University of Medicine & Dentistry of New Jersey

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Special Points of Interest:

P&T Update

Formulary Addition/Deletion

Acetaminophen injection (Ofirmev™) is a non-salicylate antipyretic and non-opioid analgesic FDA approved for the management of mild to moderate pain, management of moderate to severe pain with adjunctive opioid analgesics and reduction of fever. The risk of hepatotoxicity was emphasized given the patient population of The University Hospital, which has a high prevalence of subclinical hepatitis, including hepatitis C and alcohol use. Another concern was the potential for overdose with the possible combination of intravenous acetaminophen with oral acetaminophen in both inpatient and outpatient settings. Formulary addition of acetaminophen injection with restriction to the Anesthesiology Service in the Doctor's Office Center (DOC) Same Day Surgery suites for a maximum of 2 doses. – Approved

Policies and Procedures Update

1. 707-400-108 Resuscitation equipment checks & exchanges policy - revised
   Revisions to the resuscitation equipment checks & exchanges policy were presented for member review and approval. The code cart content list has been updated. – Approved
2. Malignant hyperthermia cart contents – new
   The malignant hyperthermia cart content policy was presented for member review and approval. – Approved
3. 707-500-122 Automatic therapeutic exchange policy – revised
   The interchange of extended-release carvedilol to immediate release carvedilol was proposed based on FDA approved dosage conversions. – Approved
4. 707-600-120 Patient's personal medication and use of medications acquired by a practitioner policy – revised
   The policy specifies that physicians/practitioners are not permitted to bring patient medications into the hospital. – Approved
5. 707-700-106 Who may administer medications policy – revised
   Radiology technicians and nuclear medicine technicians were added to the list of personnel permitted to administer medications. – Approved
6. Administration of time critical scheduled medications policy – new
   Policy addresses the timing of medication administration required by the Centers for Medicare and Medicaid Services (CMS). – Approved
7. 707-400-103 Sample Medication – revisions to the Sample Medication Procedure and Policy to add the OB/GYN clinic to the list of ambulatory clinics allowed to provide sample medication. Due to this revision the OB/GYN clinic received approval to the request filed on 12/17/12 to provide prenatal vitamins as sample medications to their pregnant and lactating patients. – Approved

SENTINEL EVENT ALERT: "Safe Use of Opioids"

On August 8, 2012, the Joint Commission (TJC) issued a Sentinel Event Alert concerning the safe use of opioids in hospitals. This type of alert identifies specific sentinel events, describes their underlying causes, and provides suggestions to prevent their occurrence in the future. There are numerous problems pertaining to opioid use including under/overprescribing, tolerance, dependence, and drug abuse. These can arise with any of the opioids e.g. fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, and sufentanil. Opioid use is considered safe in most patients, but is associated with adverse effects including respiratory depression, nausea, vomiting, constipation, sedation, dizziness, delirium, hallucinations, hypotension, and aspiration pneumonia. This article will focus on the safe use of opioids in the inpatient hospital setting.

From 2004-2011, of the opioid-related events reported to the Joint Commission's Sentinel Event Database, some included wrong dose medication errors, improper patient monitoring and other factors. The corresponding percentages are as follows: 47% due to wrong dose medication errors, 29% were related to improper patient monitoring, and 11% were related to other factors, such as excessive dosing and drug-drug interactions. TJC states that when opioids are administered, opioid-induced respiratory depression should constantly be monitored for the following reasons:

- The risk of respiratory depression increases with higher opioid doses.
- The incidence of adverse drug events may be greater than what is reported.
- Certain patients at higher risk require monitoring, including those with sleep apnea, the morbidly obese, the very young, the elderly, the critically ill, and those concomitantly receiving central nervous system and respiratory depressants.[3]

In order to safely administer opioids in a hospital setting, two important things need to be implemented: use of an accurate pain assessment tool and the application of appropriate pain management techniques.[2,4] In 2001, TJC instituted a set of pain management standards which increased awareness of safe and effective pain control.[5] In light of the necessity to appropriately manage pain, organizations should instruct their staff on several factors that can assist in the prevention of accidental opioid use, including:

• Screen patients for risk factors for respiratory depression (see above) • Assess patient history of possible analgesic use/abuse • Rule out the possibility of current use of a fentanyl patch, implanted drug delivery system, or pump before administering a new opioid • Use an individualized and multi-modal approach e.g. psychological support, nonpharmacologic therapy	• Consider a carefully titrated short-term trial for opioid-naïve patients • Consult either a pharmacist or pain specialist when converting between opioids • Avoid rapid dose escalation in opioid-tolerant patients • Take special precautions when transferring patients between care units and facilities • Avoid using opioids to meet arbitrary pain ratings or planned discharge dates

Evidence-based actions suggested by TJC

In order to avoid adverse events associated with the use of opioids, TJC provides the following recommendations to hospitals:

1. Create policies for monitoring patients receiving opioid therapy including assessing quality and adequacy of respiration and depth of sedation. Use pulse oximetry to monitor oxygenation as well as capnography to monitor ventilation.[6]
2. Implement procedures that allow for a review by a pain management specialist or pharmacist especially when dealing with high-risk opioids i.e. methadone, fentanyl, IV hydromorphone and meperidine.
3. Form policies for tracking and analyzing opioid-related incidents for quality improvement purposes.
4. Use information technology as a monitoring tool for prescribing practices:
   - Incorporate red flags or alerts into e-prescribing
   - Separate look-alike and sound-alike drugs and use tall-man lettering
   - Use programs to calculate dose conversions

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SENTINEL EVENT ALERT

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- Utilize patient-controlled analgesia (PCA) to reduce the risk of oversedation

5. Advise clinicians to use both pharmacologic and nonpharmacologic alternatives (i.e. physical therapy, acupuncture, massage, ice, music therapy).
6. Train and assess staff on effects of opioids, differences between ventilation and oxygenation, and technological and clinical monitoring.
7. Educate patients and caregivers regarding:
   - Various generic/brand names and routes of administration
   - Risks and side effects of opioids
   - Impact of opioids on psychomotor and cognitive function e.g. driving
   - Potential serious interactions with ethanol and other CNS depressants
   - Risk of tolerance, dependence, addiction and withdrawal
   - Potentiating effects when used in combination with other opioids
   - Safe and secure opioid analgesic storage at home
8. Assess the organization's need for training based on analysis of reported adverse events, near misses and staff observations.
9. Provide necessary tools to screen patients for the risk of oversedation and respiratory depression. The following tools are available for the acute care setting:
   - Pasero Opioid-Induced Sedation Scale (POSS)
   - Richmond Agitation-Sedation Scale (RASS)

The following tools can be utilized after discharge:

- Screener and Opioid Assessment for Patients with Pain (SOAPP)
- Opioid Risk Tool (ORT)
- Screening Instrument for Substance Abuse Potential (SISAP)[6]

References:

1. The Joint Commission. Safe use of opioids in hospitals. The Joint Commission Sentinel Event Alert. 2012 Aug 8;Issue 49. Available from: http://www.jointcommission.org/sea_issue_49/.
2. Vila H Jr, Smith RA, Augustyniak MJ, et al. The efficacy and safety of pain management before and after implementation of hospital-wide pain management standards: Is patient safety compromised by treatment based solely on numerical pain ratings? Anesth Analg, 2005 Aug;101(2):474-80.
3. Jarzyna D, Jungquist CR, Pasero C, et al. American Society for Pain Management Nursing guidelines on monitoring for opioid-induced sedation and respiratory depression. Pain Manag Nurs, 2011 Sep;12(3):118-145.e10.
4. Centers for Disease Control and Prevention. Emergency department visits involving nonmedical use of selected prescription drugs – United States, 2004 - 2008. Morbidity and Mortality Weekly Report. 2010 Jun, 59(23):705-709.
5. Dahl JL, Gordon DB. Joint Commission pain standards: a progress report. APS Bulletin. 2002;12(6). Available from: http://www.ampainsoc.org/pub/bulletin/nov02/poli1.htm.
6. Pasero C, McCaffery M. Pain assessment and pharmacologic management 1st ed. St. Louis: Mosby Elseveir; 2011.
7. Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. The Journal of Pain. 2009 Feb; 10(2):113-130.

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Multistate Fungal Meningitis Outbreak

On September 18, 2012, the Tennessee Department of Health was notified by a clinician regarding a patient diagnosed with *Aspergillus fumigatus* meningitis 46 days post epidural steroid injection. The Tennessee Department of Health then started an investigation in collaboration with Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA), and identified additional cases of fungal meningitis as well as basilar stroke, spinal osteomyelitis and septic arthritis/osteomyelitis of the peripheral joints. The multistate fungal meningitis outbreak has affected 20 states across the US and approximately 50 deaths have been confirmed thus far. The infections were caused by the epidural/paraspinal injection of contaminated methylprednisolone acetate manufactured by New England Compounding Center, a compounding pharmacy based in Framingham, Massachusetts. These injections were primarily used for the management of back pain, but patients have also received the injections for pain associated with the ankles, knees, hips, or shoulders. According to the FDA and the CDC, the causative organism in confirmed cases of fungal meningitis is a fungus known as *Exserohilum rostratum. E. rostratum* is a common mold found in soil and on plants. Although *E. rostratum* rarely causes infections, it has been reported to cause cases of sinusitis, skin infections, endocarditis, and osteomyelitis (rare).[4] In addition to cases of *E. rostratum* infection, one

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Multistate Fungal Meningitis Outbreak

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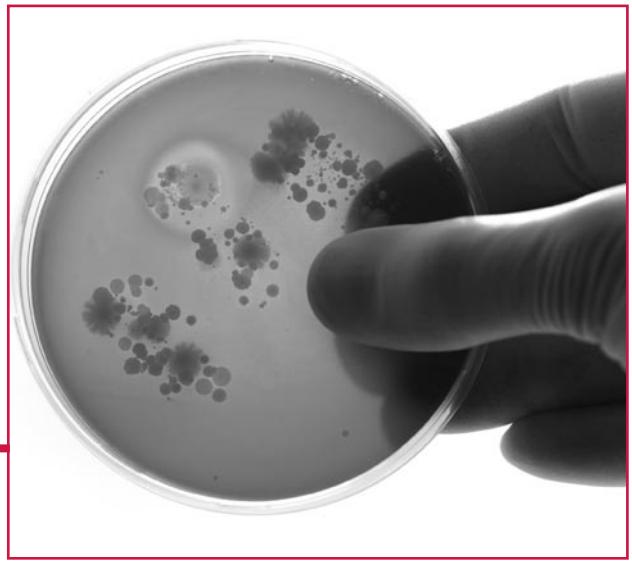
patient was identified with *Aspergillus fumigatus* and another with *Cladosporiu.*[1,2,3] The investigation is currently still ongoing and additional products (e.g. betamethasone injectable, cardioplegia solution) have been identified that are contaminated with bacteria.



Meningitis infections are very rare complications as a result of epidural/paraspinal injections. Most often, these infections are caused by bacteria and rarely by fungi. What is most troubling is the fact that patients with fungal meningitis present with nonspecific signs and symptoms (e.g. fever, headache, nausea/vomiting and photophobia). Moreover, in the current outbreak, patients either presented with, or later developed, a stroke. Thus, clinicians should be vigilant of this atypical presentation of fungal meningitis during the outbreak because early identification and treatment will reduce the risk of stroke as well as death.[1]

The CDC has developed interim treatment guidelines for central nervous system (CNS), parameningeal, and osteoarticular infections associated with injection of contaminated steroid products. The current recommendation for CNS and parameningeal infections is to initiate empiric antifungal therapy with voriconazole 6mg/kg every 12 hours. Intravenous administration of voriconazole is recommended initially with a transition to oral therapy once the patient is clinically stable. Voriconazole trough levels should be collected on the 5th day of voriconazole treatment and the dose should be adjusted to target a trough of 2-5 mcg/ml; serum levels should be then collected once per week for the next 4-6 weeks. Clinicians should also monitor for signs and symptoms of hepatotoxicity and neurotoxicity. The addition of liposomal amphotericin B should be considered in patients presenting with severe disease or for those who do not respond to voriconazole monotherapy. The recommended dose of liposomal amphotericin B is 5 to 6 mg/kg IV daily (7.5 mg/kg IV daily may be considered for patients who are not clinically improving). Signs/symptoms of nephrotoxicity (including increased Serum Creatinine (SCr), potassium and magnesium) should be monitored. For symptomatic patients who have white blood count of 5 or less in the cerebrospinal fluid, empiric antifungal therapy is not warranted.[2]

The CDC recommendations for the treatment of osteoarticular infections associated with injection of contaminated steroid products are similar to the recommendations for treating fungal meningitis. The only difference is the voriconazole dosing; for osteoarticular infections, the recommended dose of voriconazole is loading dose of 6 mg/kg every 12 hours for two doses, followed by 4 mg/kg every 12 hours. For both of those infections, a minimum of 3 months of antifungal treatment should be considered; however, this will vary depending upon individual patient factors (e.g. disease severity, comorbid conditions, etc).[3,5]

The University Hospital Pharmacy Department has never outsourced any products from New England Compounding Center (NECC). We only use Pharmedium and CAPS for outsourcing of select products. We ensure that both of these agencies adhere to strict quality control.

References:

1. Kauffman CA, Pappas,PG and Patterson TF. Fungal Infections Associated with Contaminated Methylprednisolone Injections—Preliminary Report. *N Engl J Med* 2012. [Epub ahead of print]
2. Centers for Disease Control and Prevention: Interim Treatment Guidance for Central Nervous System (CNS) and Parameningeal Infections Associated with Injection of Contaminated Steroid Products. http://www.cdc.gov/hai/outbreaks/clinicians/guidance_cns.html. Accessed October 28, 2012.
3. Centers for Disease Control and Prevention: Interim Treatment Guidance for Osteoarticular Infections Associated With Injection of Contaminated Steroid Products. http://www.cdc.gov/hai/outbreaks/clinicians/interim_guidance _ osteoarticular_infections.html. Accessed October, 28 2012.
4. Adler A, Yaniv I, Samra Z, Yacobovich J, Fisher S, Avrahami G, et al. *Exserohilum:* an emerging human pathogen. Eur J Clin Microbiol Infect Dis 2006;25(4):247-253.
5. Vfend [package insert]. New York: Pfizer, Inc; 2002.

By: Engy Ibrahem, PharmD Candidate 2013, Rutgers University

HIV Management and the Evolving Guidelines

Since the development of the first antiretroviral drug over 25 years ago, the treatment of human immunodeficiency virus (HIV) has made leaps and bounds. In recent years, a number of evidence based findings have led experts to review and amend existing guidelines for HIV management in the 2012 Recommendations of the International Antiviral Society.

One pertinent change concerns the age old question of when to begin antiretroviral therapy (ART) in patients. Practitioners, for years, have been trying to weigh the advantages of early viral suppression and the disadvantages related to medication toxicity, increasing drug resistance, costs etc. However, in light of recent data, experts recommend that all HIV-infected patients should be offered ART regardless of the CD4 count (CD4 cell count of 500/mL and below is a strong recommendation; CD4 cell count above 500/mL is a moderate recommendation based on limited data).[1]

Additional revisions in the recent guidelines include the moderate recommendation to treat patients who are acutely infected by HIV, regardless of symptoms. Two randomized clinical trials support this change by demonstrating a delayed rate in CD4 cell decline in recently diagnosed patients with immediate versus deferred ART. Strategically offering early treatment can prevent the spread of infection within a patient population that is at significant risk for transmitting the disease.[1] Furthermore, it is strongly recommended for patients who have been co-infected with opportunistic infections to start ART within the first 2 weeks of diagnosis unless the coexisting infection is cryptococcal meningitis or tuberculosis (TB). Studies have shown that initiating ART during cryptococcal treatment may result in an increased incidence of mortality.[1,2] In addition, trials have evaluated HIV treatment initiation in TB patients and, as the data suggests, patients with CD4 cell count below 50/mL should be started on ART within 2 weeks and those with a higher CD4 cell count should be started by 8 to 12 weeks.[1] A recent trial evaluating the decision of beginning ART in patients with TB meningitis had inconclusive results and the guidelines currently recommend starting therapy within 2 to 8 weeks for these patients.[3]

Along with changes in HIV treatment initiation, additional recommendations regarding medications have also been made. Many of the recommendations revolve around new treatment options that have been approved for market in recent years. One such medication, rilpivirine, a non-nuleoside reverse transcriptase inhibitor (NNRTI), has been added as an alternative component of the ART regimen for initial treatment. Furthermore, a co-formulation which includes a new integrase inhibitor with booster (elvitegravir/ cobicistat) along with nucleoside reverse transcriptase inhibitors (tenofovir/ emtricitabine) as a once a day regimen has been added as an alternative initial treatment option. Changes have also been made to the existing regimens. Abacavir/ lamivudine has been switched to a preferred component of initial ART in patients with HIV-1 RNA levels <100,000 copies/mL. Additionally, a tolerability related change has been made with the recommendation to avoid tenofovir in postmenopausal women due to the concern for an increased risk of fractures in this patient population.

Overall, the new international guidelines reflect the current

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A look into the evidence…

TRIAL	RESULTS
HIV- CAUSAL Collaboration (Observational) and CASCADE (Observational cohort)[4,5]	Support starting ART when CD4 cell count drops below 500 cells/mL: slower disease progression, increased AIDS free survival.
COHERE (Observational cohort)[6]	Higher CD4 cell count after virologic suppression (Initial CD4 cell count up to 500/mL): Decreases risk of AIDS events, all-cause mortality, and non-AIDS mortality Higher CD4 cell count after virologic suppression (Initial CD4 cell count above 500/mL) Slightly reduced risk of disease progression
HIV Prevention Trials Network (HPTN) 052 study (Phase III, two-arm, randomized, controlled, multi-center trial)[7]	Initiating therapy in HIV-serodiscordant couples (CD4 cell counts 350/mL-550/mL) led to: 41 percent reduction in World Health Organization (WHO) stage 4 events (TB, bacterial infections, death)
Early versus delayed initiation of ART in HIV co-infected with cryptococcal meningitis (Prospective open –label randomized clinical trial)[2]	ART begun within 72 hours versus after 10 weeks of treatment for cryptococcal meningitis: Risk of death 2.85 times higher in early ART group
Timing of initiation of antiretroviral therapy in HIV associated tuberculous meningitis (Randomized double-blind placebo controlled trial)[3]	ART begun within 2 versus 8 weeks of treatment for TB meningitis: Did not show improved survival Low generalizability: high injection drug use patient population Most deaths occurred within first month (perhaps associated with severity of meningitis and not directly related to ART)

HIV Management and the Evolving Guidelines

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practice recommendation in the United States. The guidelines from the Department of Health and Human Services (DHHS) also recognize the importance of initiating treatment early, and recommend ART for all infected individuals. However, the treatment of acute HIV infection (seroconversion within past 6 months) remains optional. With regard to starting ART in patients co-infected with TB, the recommendations mirror the international guidelines except in patients who have a greater severity of disease and a CD4 cell count >50µL. These patients should be initiated on ART within 2 to 4 weeks regardless of the CD4 cell count. In addition, and not unlike the international recommendations, the DHHS guidelines state that practitioners may consider a short delay in initiating ART in patients with cryptococcal meningitis and nontuberculous mycobacterium since they are at an increased risk for developing complications. Lastly, the ART regimens have also been revised to add rilpivirine and Elvitegravir/cobicistat/tenofovir/emtricitabine as alternative options for ART-naïve patients.[8]

The changes that have been made to the current guidelines demonstrate the ever-evolving nature of HIV management and new data continues to shed light on unanswered clinical questions.

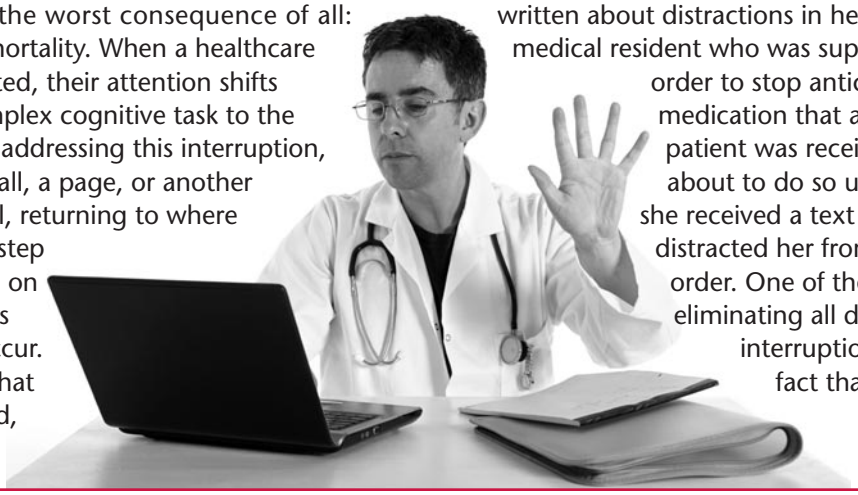
References:

1. Thompson MA, Aberg JA, Hoy JF, et al. Antiretroviral Treatment of Adult HIV Infection: 2012 Recommendations of the International Antiviral Society–USA Panel. *JAMA.* 2012;308(4):387-402.
2. Makadzange AT, Ndhlovu CE, Takarinda K, et al. Early vs delayed initiation of antiretroviral therapy for concurrent HIV infection and cryptococcal meningitis in sub-Saharan Africa. *Clin Infect Dis.* 2010;50(11):1532-1538
3. Török ME, Yen NT, Chau TT, et al. Timing of initiation of antiretroviral therapy in human immunodeficiency virus (HIV) – associated tuberculous meningitis. *Clin Infect Dis.* 2011;52(11):1374-1383
4. Cain LE, Logan R, Robins JM, et al. HIV-CAUSAL Collaboration. When to initiate combined antiretroviral therapy to reduce mortality and AIDS-defining illness in HIV-infected persons in developed countries: an observational study. *Ann Intern Med.* 2011;171(17):1560-69.
5. Jonsson M, Fusco JS, et al; Writing Committee for the CASCADE Collaboration. Timing of HAART initiation and clinical outcomes in human immunodeficiency virus type 1 seroconverters. *Arch Intern Med.* 2011;171(17):1560-69.
6. Opportunistic Infections Project Team of the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) in EuroCoord. CD4 cell count and the risk of AIDS or death in HIV-Infected adults on combination antiretroviral therapy with a suppressed viral load: a longitudinal cohort study from COHERE. *PLoS Med.* 2012;9(3):e1001194
7. Cohen MS, Chen YQ, McCauley M, et al; HPTN 052 Study Team. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med.* 2011;365(6):493-505
8. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Washington, DC: Department of Health and Human Services, 2012:1-239.

By: Linda Johnson, PharmD Candidate 2013, Rutgers University

Distracting Healthcare Professionals Can Result in Fatal Mistakes

Distractions can result in errors in any profession, some causing monetary or time consuming consequences; however, in health care professions distractions can cause the worst consequence of all: patient morbidity or mortality. When a healthcare professional is interrupted, their attention shifts from their primary complex cognitive task to the interrupting task. After addressing this interruption, whether it is a phone call, a page, or another health care professional, returning to where they were in the multi-step task they were working on becomes difficult; this is where mistakes may occur. This is due to the fact that once attention is shifted, memory loss of the primary task occurs to make room for the thoughts required to handle the interrupting task. A story that is often cited in many research articles written about distractions in health care is that of a medical resident who was supposed to send an order to stop anticoagulation medication that a post-operative patient was receiving but as she was about to do so using her smart phone she received a text message which distracted her from ever sending the order. One of the reasons that eliminating all distractions or interruptions is difficult is the fact that not all of the



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Distracting Healthcare Professionals

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interruptions are bad. For instance, sometimes physicians are paged to clarify or change orders that they have written; their timely response to these pages not only results in the patient receiving the correct medication but to also receive it in a timely manner.

When it comes to distractions by handheld devices, like smart phones and tablets, the discussion becomes difficult because these same devices that have helped save lives due to the ability to instantly access patient charts and prescription information, can result in fatal errors when not used correctly. According to one practice-focus research paper that researched the effects of smart phones in the health care setting, the writers state that the although smart phones have a great benefit in assisting in patient treatment, their overuse or abuse can actually severely undermine any benefit. The same study states that cell phones can be detrimental to cognitive performance by increasing reaction time, reducing focus, and lowering performance of tasks needing mental concentration and decision making. Professionals have admitted to taking personal phone calls and texting during procedures that require their undivided attention.

Many implementations have been suggested, made, and studied to show a significant improvement in distractions to health care professionals. These include designating "distraction free areas"; these can be areas where nurses mix medications, or where any other complex, error prone procedures are performed. In these areas, use of handheld devices is to be forbidden and no one should speak to anyone performing any task requiring the professional's undivided attention. Checklists or "To-do" lists in rooms where complex tasks and procedures are to be performed have helped significantly because it allows the professional to return to the task and know exactly where he or she left off and continue without error. Other suggestions have included professionals making alerts on their phones that only go off for contacts that are designated as important to respond to while they are working, and for nurses to wear vests that designate when they cannot be disturbed, these two however have been both difficult to implement and enforce. Overall it is important as a health care professional to remember that patients are the number one priority and when you are working, minimizing distractions can be what makes the difference between life and death.

References:

Matt Richtel. "As Doctors Use More Devices, Potential for Distractions Grows". New York Times. 15 December 2011.

A. Joy Rivera, Ben-Tzion Karsh. "Interruptions and Distractions in Healthcare: Review and Reappraisal". Qual Saf Health Care. 2010 August; 19(4):304-312. Published online 2010 April 8.

Preetinder S. Gill, Ashwini Kamath, Tejkaran S. Gill. "Distraction: an assessment of smartphone usage in health care work settings". Risk Management Healthc Policy. 2012; 5:105-114. Published online 2012 August 27.

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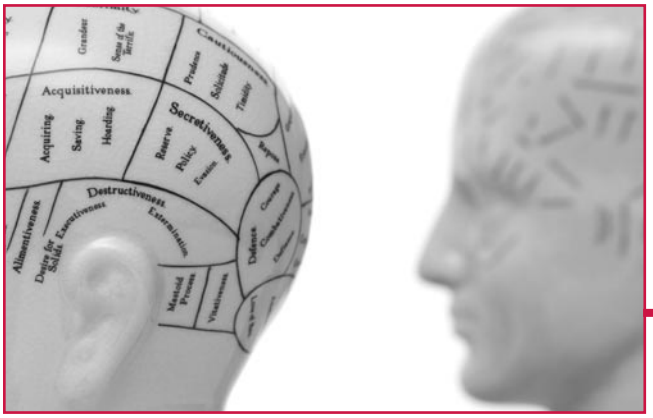
Schizophrenia and the Use of Antipsychotic Combination Therapy

Schizophrenia is a chronic brain disorder often presenting as disorganized thoughts, delusions, and hallucinations, with impaired psychosocial function and inappropriate affect. Due to the nature of the disorder, pharmacotherapy focuses on the management of symptoms. The mainstay of schizophrenia treatment is antipsychotic therapy, which serves to decrease and manage symptoms to improve patients' functionality and quality of life. The choice of antipsychotic is determined based on the patient's clinical characteristics; however, inadequate response is often a challenge that arises with schizophrenia pharmacotherapy. In fact, up to 30% of patients will have little to no response while



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Schizophrenia and the Use of Antipsychotic

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another 30% will experience improvement with lingering symptoms.

Though there is insufficient evidence to support combining antipsychotics, the use of multiple antipsychotics has increased in clinical practice. Because atypical antipsychotics have different mechanisms of action, clinicians often find the use of multiple antipsychotics justified. There exist only a few randomized controlled trials that study the benefits of combination therapy over monotherapy. These trials demonstrated a slight benefit with combination therapy based on improvements in standard psychometric rating scales; however, the combination therapies that were studied included clozapine plus a first-generation agent. One study of risperidone given concomitantly with quetiapine yielded negative results. To replicate what typically occurs in clinical practice, more studies would need to investigate the use of a combination of atypical antipsychotics.

There are a few clinical scenarios in which it is acceptable for a patient to be on dual antipsychotic therapy. One circumstance is when a patient requires a switch in antipsychotic due to inadequate response or side effects. In this instance, cross-tapering is recommended and thus there is a period of time where the old antipsychotic over-laps with the new. In patients where dose-limiting adverse events are experienced, it may be required to combine low doses of two agents with differing side effect profiles (Table 1). This combination allows the limitation of dose-related side effects while providing additive dopamine blockade.

Because limited data support the benefit of combination therapy over monotherapy, clinicians should consider other factors or contributors of inadequate response before initiating combination therapy. Underdosing, drug interactions, or poor adherence are some factors that should be assessed. Should combination therapy be initiated, patients should be monitored closely for side effects and for efficacy. Since about two-thirds of patients are successfully converted to monotherapy, gradual discontinuation of one agent should be considered once a patient has been stable for at least three months.

Overall, no specific combination of antipsychotics can be recommended due to the lack of evidence. It is theorized that agents that act at different receptors may prove to be good combinations. Agents with different side effects profiles should also be considered. More controlled studies comparing the use of multiple antipsychotics versus monotherapy need to be performed before a conclusive recommendation can be made. Such studies should investigate combination therapy with antipsychotics of differing side effect profiles or differing mechanisms of action and should analyze the benefits of using such combinations. Until more controlled trials are published, clinicians should assess the individual patient need for multiple antipsychotics and weigh the risks and benefits to combination therapy.

References:

1. PL Detail-Document, Combining Antipsychotics in Schizophrenia. Pharmacist's Letter/Prescriber's Letter. October 2012.
2. Correll CU, Rummel-Kluge C, Corves C, et al. Antipsychotic combinations vs monotherapy in schizophrenia: a meta-analysis of randomized controlled trials. Schizophr Bull 2009;35:443-57.
3. Zink M. Augmentation of olanzapine in treatment-resistant schizophrenia. J Psychiatry Neurosci 2005;30:409-15

By: Lorraine Green Pharm. D. Candidate 2013

Table 1. Comparison of Antipsychotics

Antipsychotic	Weight Gain	Diabetes Risk	Dyslipidemia	QT Prolonging	CYP3A4 Metabolism	Sedation
Aripiprazole	Low to none	None	None	Yes	Yes	Low
Asenapine	Low to none	Low to none	Low to none	Yes	Yes (minor)	Low to Moderate
Clozapine	High	High	High	Yes	Yes	High
Iloperidone	Moderate	Low	Low	Yes	Yes	Low
Lurasidone	Low	Low	Low or none	No	Yes	Moderate
Olanzapine	High	High	High	Yes	No	Moderate
Paliperidone	Low	Low	None	Yes	Yes (minor)	Low
Quetiapine	Moderate	Moderate	Moderate	Yes	Yes	Moderate
Risperidone	Moderate	Moderate	Low	Yes	No	Low
Ziprasidone	Low or none	None	None	Yes	Yes	Low