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TODAY'S TOPIC:

Getting to the Heart of the Cardiovascular Effects of CNS Stimulants

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Background:

The CNS stimulants including: methylphenidate (Ritalin®), dextroamphetamine (Dexedrine®) and mixed amphetamine salts (Adderall®) are medications often used off-label for the management of fatigue and depression in patients with palliative care needs. Unfortunately, these medications have been linked to significant cardiovascular risks in patients with both a known cardiac history, and without cardiac disease. These medications are thought to improve the symptoms of fatigue and depression, as well as increase the risk of these adverse effects, through activation of the brain stem arousal system and cortex.

Per the package insert of Ritalin, there is a risk of serious cardiovascular events with the administration of these medications:

Serious Cardiovascular Events

Sudden Death and Preexisting Structural Cardiac Abnormalities or Other Serious Heart Problems

Adults

Sudden death, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. Although the role of stimulants in these adult cases is also unknown, adults have a greater likelihood than children of having serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems. Adults with such abnormalities should also generally not be treated with stimulant drugs.

If you have a topic you would like the pharmacy team to answer, please send your suggestions to: pruskowskija@upmc.edu

These medications have been known to have the following cardiovascular changes: 1. pulse increases of 3 to 10 bpm; 2. SBP increases of 3-8 mmHg; and 3. DBP increases of 2-14 mmHg. These effects do not appear to diminish with time. However, as above, they have also been connected to sudden death, stroke, and MI. In fact, in 2011 the FDA published a Drug Safety Communication regarding the use of these medications for ADHD in children and young adults (see here for more).

Importance:

It is important for palliative care providers to be aware of the cardiovascular risks of the CNS stimulants, to best prescribe these medications rationally.

The Literature:

There is limited literature regarding these effects in palliative care patients. Therefore literature will be extrapolated from other studies. Unfortunately, there are mixed results.

- JAMA. 2011 Dec 28;306(24):2673-83.
  ADHD medications and risk of serious cardiovascular events in young and middle-aged adults.
  - Objective: To examine whether current use of medications prescribed primarily to treat ADHD is associated with increased risk of serious cardiovascular events in young and middle-aged adults
  - Methods: Retrospective, population-based cohort study using electronic health care records from 4 study sites (OptumInsight Epidemiology, Tennessee Medicaid, Kaiser Permanente California, and the HMO Research Network), starting in 1986 at 1 site and ending in 2005 at all sites
  - Results: During 806,182 person-years of follow-up (median, 1.3 years per person), 1357 cases of MI, 296 cases of SCD, and 575 cases of stroke occurred:
    - There were 107,322 person-years of current use (median, 0.33 years), with a crude incidence per 1000 person-years of 1.34 (95% CI, 1.14-1.57) for MI, 0.30 (95% CI, 0.20-0.42) for SCD, and 0.56 (95% CI, 0.43-0.72) for stroke
    - The adjusted RR for current use vs remote use was 1.03 (95% CI, 0.86-1.24); for new use vs remote use, the adjusted RR was 1.02 (95% CI, 0.82-1.28); the upper limit of 1.28 corresponds to an additional 0.19 events per 1000 person-years at ages 25-44 years and 0.77 events per 1000 person-years at ages 45-64 years
  - Conclusions: "Among young and middle-aged adults, current or new use of ADHD medications, compared with nonuse or remote use, was not associated with an increased risk of serious cardiovascular events."
  - *Discussion:* So no connection?...

- Am J Psychiatry. 2012 Feb;169(2):178-85.
  Methylphenidate and risk of serious cardiovascular events in adults.
  - Objective: To explore whether the use of methylphenidate in adults is associated with elevated rates of serious cardiovascular events compared with rates in nonusers.
  - Methods: Cohort, case-controlled study of new users of methylphenidate based on administrative data from a five-state Medicaid database and a 14-state commercial insurance database. All new methylphenidate users with at least 180 days of prior enrollment were identified. Users were matched on data source, state, sex, and age to as many as four comparison subjects who did not use methylphenidate, amphetamines, or atomoxetine.
  - Results: A total of 43,999 new methylphenidate users were identified and matched to 175,955 nonusers.
    - The age-standardized incidence rate per 1,000 person-years of sudden death or ventricular arrhythmia was 2.17 (95% CI=1.63-2.83) in methylphenidate users and 0.98 (95% CI=0.89-1.08) in nonusers, for an adjusted hazard ratio of 1.84 (95% CI=1.33-2.55).
    - Dosage was inversely associated with risk.
    - Adjusted hazard ratios for stroke, myocardial infarction, and the composite endpoint of stroke or myocardial infarction did not differ statistically from 1.
  - Conclusions: "Although initiation of methylphenidate was associated with a 1.8-fold increase in risk of sudden death or ventricular arrhythmia, the lack of a dose-response relationship suggests that this association may not be a causal one."
  - *Discussion:* Remember this was a retrospective design, so the data could have been confounded. Additionally, the authors noted that the inverse relationships

between dosage and the rates of stroke, myocardial infarction, the composite outcome of stroke and myocardial infarction, and all-cause death. This may have suggested that lower dosages were prescribed to the frailest patients who might have had the greater risk, so the results may have been affected by unmeasured confounding

As above, little data exists regarding these risks specifically in the palliative care population. Here is one that I will highlight:

- PLoS One. 2014 Jan 8;9(1):e84391.
  Effect of methylphenidate in patients with cancer-related fatigue (CRF): a systematic review and meta-analysis.
  - Findings: Despite a large placebo effect observed in the studies included, pooled data suggested therapeutic effect of methylphenidate on CRF
    - Of 5 studies included, the adverse effects were described in 4.9% of patients in methylphenidate group and 1.6% of patients in placebo group. The overall risk ratio for study discontinuation due to side effects didn't suggest statistical significance between patients treated with methylphenidate and patients with placebo (RR 2.38, 95% CI 0.69–8.29, p = 0.17, I^2 = 8%)
    - Table 2:

The pooled adverse effects of Methylphenidate in included studies.

Adverse effect	No. of studies	No. of patients Methylphenidate/placebo	Risk Ratio and 95%CI	P value	I^2 (%)
Tachycardia	3	96/100	0.66 [0.21, 2.06]	0.47	40
Insomnia	2	128/131	1.46 [0.78, 2.74]	0.23	0
Vertigo	2	128/131	3.74 [1.52, 9.16]	0.004	0
Anxiety	2	145/148	2.50 [1.32, 4.73]	0.005	0
Nausea	2	110/112	4.65 [1.84, 11.77]	0.001	0
Anorexia	2	121/123	2.18 [1.15, 4.14]	0.02	0

  - *Discussion:* So as you can see, tachycardia occurred. You can infer however that the duration of these studies did not allow enough time to examine the risk of sudden death, MI or stroke…

So… What does this all mean Jenn?:

- Considering that these medications are often utilized short-term, the risk of cardiovascular events may outweigh the benefits of therapy. There are groups however that I would especially caution. They are those patients with: serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems
- Lastly, remember that increases in blood pressure and tachycardia can occur, and does not diminish with time. However, I am not sure if these increases are clinically significant
- Of note, QTc prolongation has not been seen with these agents
- I would consider these agents for patients with clinically significant depression and fatigue, especially in short durations

Look forward to other PCP Phast Phacts on CNS Stimulants

CLINICAL PEARL:

The CNS stimulants have been connected with serious cardiovascular events, however the evidence is mixed. Caution should be paid to those patients with significant cardiac problems.