Report on Death Risk by SMR with Opiates and Common Adjuvant Combinations in Patients with Chronic pain.

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- D.C. Randolph MD PhD MPH

A Few Terms….

- Polypharmacy: The use of multiple medications
- Objective: Measurable (BP, pulse, MRI scan findings)
- Subjective: An unmeasurable factor (Headache, Pain, fatigue)
- Pain: "An Unpleasant Subjective Experience…."
- Validity
- Reliability
- Tenderness, spasms
- Syndrome (Humpty Dumpty, Lewis Carroll, 1865)

TERMS

- Opiates, opioids, narcotics
- “Adjuvants” Medications provided to improve opiate effect, address other symptoms (i.e. muscle relaxers, antidepressants, anxiolytics, neuroleptics)
- Chronic benign pain: Pain not due to cancer lasting over 90 days (more on this later)
- Drug combinations and drug-drug interaction potential (mild/moderate/major)

The “witches brew”…… or, What happens when you mix all these together?

- Drug-drug interactions (DDI)
- Drug A+ Drug B=????
- 3 types of POTENTIAL DDI
- “Mild”…slight irritation, not harmful
- “Moderate”….noticeable irritation potential harms but manageable
- “SEVERE”…. Mixing these 2 drugs together is potentially lethal and cannot be justified. This combination would be contraindicated.

Opiates: What do they do?

- Analgesic (pain relief)
- Euphoria (elevated mood), drowsiness, mental clouding, apathy, lessened physical activity ("psychomotor slowing")
- Anti-emetic (anti-nausea)
- Cough suppressant
- Anti-diarrheal/anti-spasmodic
- Respiratory depression (primary cause of morbidity with opiate use) *[Goodman/Gilman 2011 pg 492].*
- Central sleep apnea
- Addiction/tolerance
- Death

Current Trends (CDC WEBSITE):

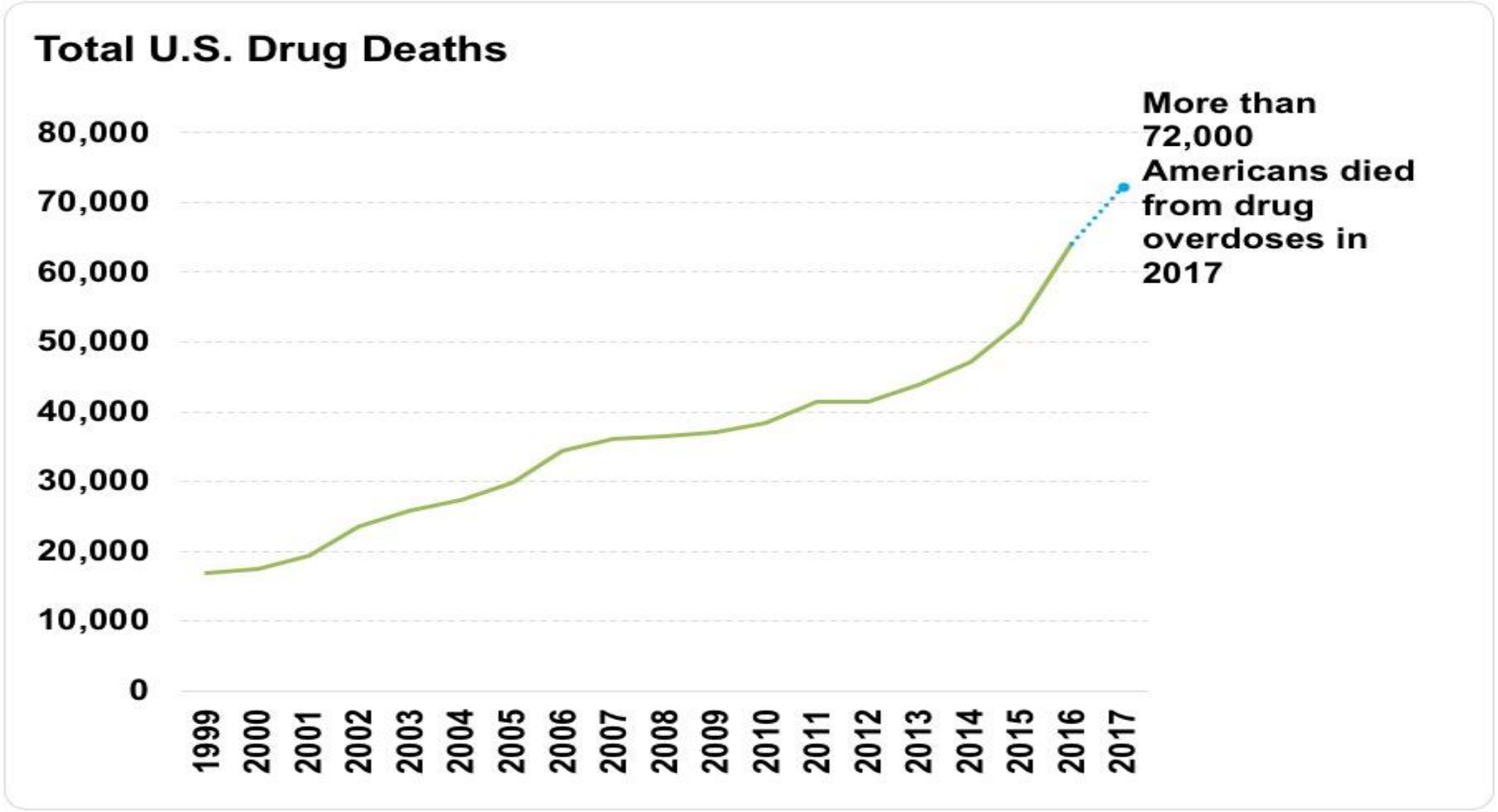
- More people died from drug overdoses in 2017 than in any year on record (approx. 73,000 in US). The majority of drug overdose deaths (more than six out of ten) involve an opioid.[1] And since 1999, the rate of overdose deaths involving opioids (including prescription opioid pain relievers and heroin) nearly quadrupled.[2] From 2000 to 2014 nearly half a million people in the US died from drug overdoses. 78 Americans die every day from an opioid overdose.
- References at end of slides.

SAMHSA (Substance Abuse and Mental Health Services Administration)

- In 2014, the rate of past year nonmedical pain reliever use among youth aged 12 to 17 was 6.2%. For young adults ages 18 to 25, the rate was 11.8%.
- In 2014, youths aged 12 to 17, or young adults aged 18 to 25, were more likely to misuse prescription drugs in the past year than adults aged 26 or older.
- The percentage of current misusers of prescription drugs significantly increased for those aged 12-17 from 2.2% in 2013 to 2.6% in 2014.
- On an average day during the past year, approximately 5000 adolescents used prescription pain relievers non-medically for the first time.

TRENDS (CDC 2018, NIH 2018)

- We now know that overdoses from prescription opioid pain relievers are a driving factor in the 16-year increase in opioid overdose deaths. Since 1999, the amount of prescription opioids sold in the U.S. nearly quadrupled, yet there has not been an overall change in the amount of pain that Americans report. Deaths from prescription opioids—drugs like oxycodone, hydrocodone, and methadone—have also quadrupled since 1999.


Total U.S. Drug Deaths
More than 72,000 Americans died from drug overdoses in 2017
80,000
70,000
60,000
50,000
40,000
30,000
20,000
10,000
0
1999
2000
2001
2002
2003
2004
2005
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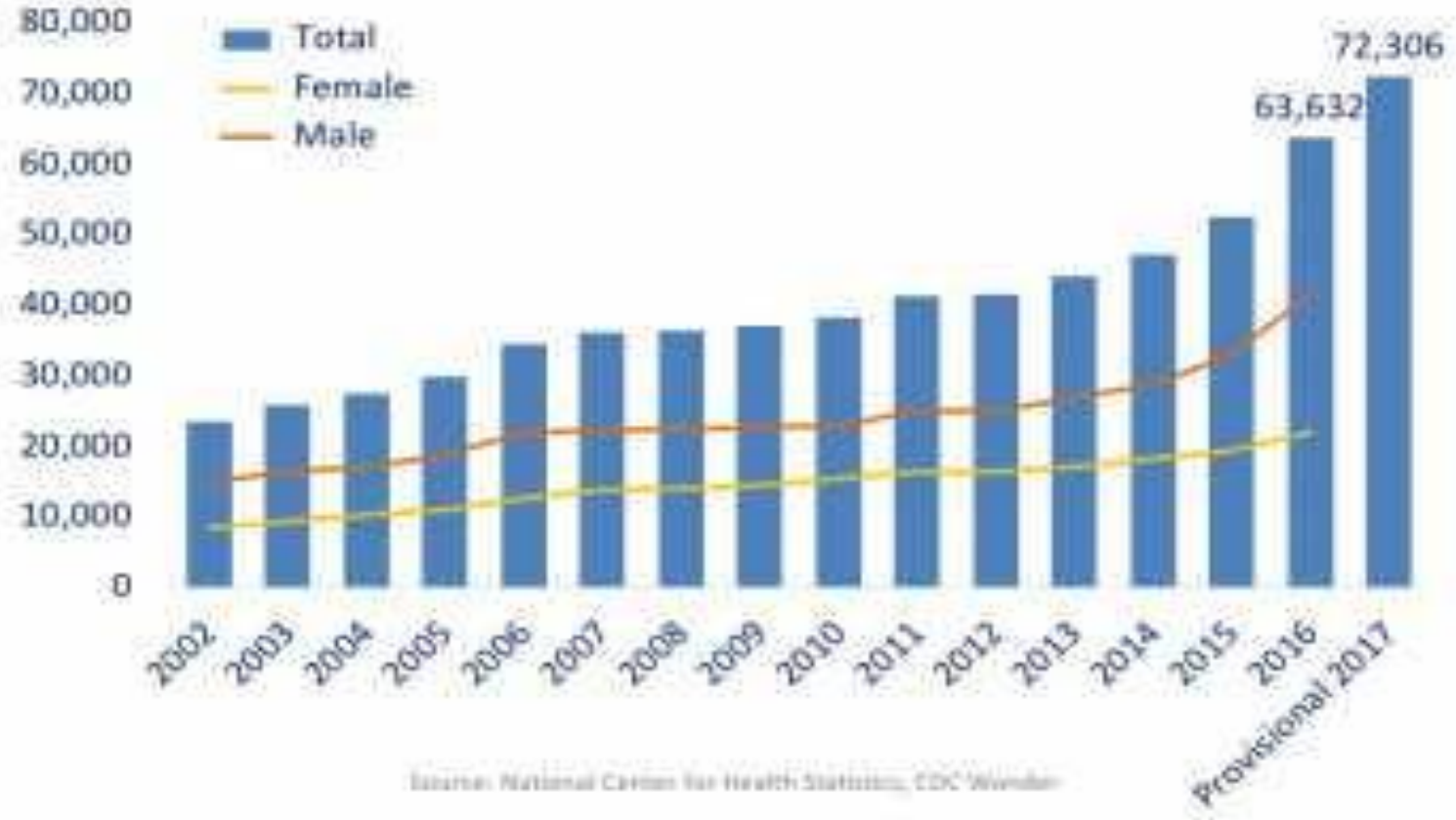
National Overdose Deaths

Number of Deaths Involving All Drugs



Why do people die from narcotics?

- The most common causes of death are CARDIAC AND RESPIRATORY SUPRESSION.
- Many narcotics, especially at higher doses and in combination with anxiolytic/sedative hypnotic drugs (Ambien, Xanax, Valium, etc.) suppress the respiratory drive in the brain stem.
- Unless a thorough post mortem exam is done (including toxicology) a drug related death could be easily missed
- Coroners may sign off cause of death due to “natural causes”
- For this reason, drug related deaths are likely UNDER REPORTED

Back to pain for a bit…

- "An unpleasant subjective experience"
- Cannot be objectively measured
- What can we measure? (BP, pulse, pulmonary/cardiac function)
- Visual analogue pain scale, oswestry all self report and unreliable
- Pain rated mild (1-3), mod (4-6), severe (7-10)
- "Severe pain" inconsistent with the ability to perform activities of daily living (drive, dress yourself, eat, etc.))AMA 4th Ed. guides, pg. 315). This would be progressive when reflected numerically.
- "Severe pain" reports in the presence of normal BP, pulse, resp. rate reflect a physiologic inconsistency.

Opiate complications

- Opiate hyperalgesia (increase in pain due to the opiate)
- Tolerance
- Opiate use disorder (“addiction”)
- Multi-system involvement is possible (cardiac, endocrine, neurologic, GI, etc.). Includes osteoporosis, fractures, decreased steroidogenesis, immunosuppression, MI, sleep apnea, bowel obstruction.(ODG)
- Polypharmacy may occur to address side effects such as somnolence, arousal disturbance, GI hypomotility, Impotence, etc.
- Drug-drug interactions may also occur with other opiates and adjuvants
- Death

How did we get here?

- Typically, a relatively minor event occurs with high reports of pain.
- A health care provider , seeking to diminish complaints, prescribes medications to address symptoms.
- Pain complaints escalate (rationale often unclear, usually underinvestigated.
- Side effects and additional symptoms are reported.
- More medication types to address side effects, and increased dose and quantity to address additional complaints.
- “Pain management” implemented
- Polypharmacy

Common Pitfalls/Risks for lesser outcomes:

- Historic inaccuracy (information incomplete or “modified”)
- Incomplete exam, workup of complaints and/or complications
- Treatment of symptoms, not underlying process
- LACK OF OBJECTIVE FINDINGS
- UDS/T (incorrectly interpreted, or not reviewed). Note a distinction between screening and testing urine for drugs.
- Pill counts? (often not done)
- Diminished physician involvement (PA, NP, MA)
- Ignorance of DDI and comorbidities
- Low index of suspicion for substance abuse/misuse
- Opioid use disorder

Opioid use disorder

A problematic pattern of opioid use that causes clinically significant impairment or distress. A diagnosis is based on specific criteria such as unsuccessful efforts to cut down or control use, as well as use resulting in social problems and a failure to fulfill obligations at work, school, or home. Opioid use disorder has also been referred to as “opioid abuse or dependence” or “opioid addiction.”

DSM V classifies this under the heading ” SUBSTANCE USE DISORDER”.

Evidence of benefit with chronic opiate use in the treatment of non malignant pain??

- Chou R, et al. Effectiveness and Risk of Long Term Opioid Therapy for chronic pain: A Systematic Review for NIH. Ann Intern Med. Feb 17 2015; 162: 4. (276-290).
- "In summary, reliable conclusions about the effectiveness of long-term opioid therapy for chronic pain are not possible due to the paucity of research to date.
- Accumulating evidence supports the increased risk for serious harms associated with long-term opioid therapy, including overdose, opioid abuse, fractures, myocardial infarction, and markers of sexual dysfunction;

  "for some harms, the risk seems to be dose-dependent. "

A Different Perspective Based on Recent Literature:

- Opioid Prescribing After Nonfatal Overdose and Association with Repeated Overdose. Larochelle, MR et al. Annals of Internal Medicine 2016,Volume 164; 1-9
- "Almost all patients continue to receive prescription opioids after a (nonfatal) overdose. Opioid discontinuation is associated with a lower risk for repeated overdose."
- Current Guidelines now state that opioid misuse and harmful effects are "compelling" reasons to discontinue opioids.
- The only significant predictors for repeated overdose were time-varying daily opioid doses and use of Benzodiazepines.

So…..are all Opiates dangerous no matter what???

- No.
- There appears to be a safe level below which complications and hazards are diminished, and pain/functional benefit obtained.
- We studied Ohio BWC claims 2000-2011, evaluating all-cause mortality among those taking opioids alone or with commonly used drug combinations. NSAIDs users represented comparison population.
- Standardized Mortality Ratios were calculated, demonstrating significant increase in death risk when schedule II drugs were used in common combinations.
- No statistically significant increased risk of mortality was noted when schedule II drugs were used alone in lower doses.

STANDARDIZED MORTALITY RATIOS Randolph, D. et al. pending publication

- This is determined through a ratio of Observed deaths/Expected Deaths
- Ohio general population is the comparison group (CDC data)
- Male and Female combined

Group	OBS Deaths	EXP	SMR	p value	95%CI
NSAIDs only	45	82.69	0.54	<0.001	(0.4,0.72)
Sch2 only	545	622.52	0.88	0.002	(0.8,0.95)
Sch2+ASH	51	36.25	1.41	0.014	(1.06,1.84)
Sch2+MR/AD	296	278.47	1.06	0.29	(0.95,1.19)
Sch2+ ASH+MR/AD	251	144.12	1.74	<0.001	(1.54,1.97)

SMR Schedule II, MED 50-100MED (Male and Female combined)

Group	OBS Deaths	EXP	SMR	p value	95%CI
NSAIDs only	45	82.69	0.54	<0.001	(0.4,0.72)
Sch2 only	142	173	0.82	0.017	(0.69,0.96)
Sch2+ASH	17	13.41	1.27	0.33	(0.76,1.99)
Sch2+MR/AD	260	155.96	1.67	<0.001	(1.47,1.88)
Sch2+ ASH+MR/AD	115	51.8	2.22	<0.001	(1.84,2.65)

SMR >100mg MED (male and female)

Group	OBS Deaths	EXP	SMR	p value	95%CI
NSAIDs only	45	82.69	0.54	<0.001	(0.4,0.72)
Sch2 only	108	104.55	1.03	0.74	(0.85. 1.24)
Sch2+ASH	13	5.91	2.2	0.0035	(1.22,3.67)
Sch2+MR/AD	300	287.27	1.04	0.45	(0.93, 1.17)
Sch2+ ASH	52	25.1	2.07	<0.001	(1.56,2.7)
MR/AD					

Key rules for medical management

- Everything we as physicians do should be safe and effective.
- There is very little science to support many of the interventions provided.
- High doses of narcotics and polypharmacy have been shown to be hazardous and rarely accompanied by meaningful functional restoration.
- Our study, as well as a number of others have demonstrated significant health hazards associated with polypharmacy
- These interventions do not appear to be safe or effective
- Continuation of these practices should be subjected to scientific scrutiny and challenge

Take home points on Polypharmacy in chronic benign pain population

- No RCT exists to support polypharmacy as sometimes seen in clinical practice
- The science to support treatment of non-malignant pain with high doses of narcotics and polypharmacy is non existent
- No peer -reviewed RCT has been done for benzodiazepines!
- If the patient does not improve in a reasonable time with provided treatment, a thorough history, physical examination and differential diagnostic process should be conducted by a board certified physician, with knowledge of current peer-reviewed literature and treatment guidelines.

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Red Flags

- Continued or Increased Pain Which Is Out of Proportion to the Physical Findings – Symptoms exceed the pathology
- Drug Seeking Behavior – ER visits; Multiple Rx Doctors
- Increasing Drug Doses Without Corresponding Improvement – where more is not better
- History of Ineffective Intervention Techniques – Patient is not getting better
- Extreme Pain Medication Beyond the Recovery Period
- Insufficient Objective Support for Subjective Complaints

Medical Treatment Guidelines: approaches to assure appropriate use of narcotics/opioids

- Screening for potential alcohol and drug abuse problems as well as co-morbid psychiatric conditions to identify those who may be prone to dependence or abuse.
- Long-term narcotics should only be offered after other therapies have failed to improve function.
- Monitor using periodic, random urine drug tests.
- Periodic re-evaluation of function and side effects as well as a psychiatric assessment.
- Tapering and discontinuance when patient goals are not being met.

Prescription Drug Monitoring Programs

- Currently, 48 states either have operating PDMP's, or have passed legislation to implement them. Additionally, Missouri and New Hampshire have legislation pending to establish a PDMP's. Programs vary from state to state in their operations and in terms of which drugs are subject to monitoring, but the collection of data is meant to prevent abusers from obtaining prescription from multiple doctors, also known as "doctor-shopping".