A Retrospective Analysis of Concurrent Benzodiazepine and Opioid Toxicity Mortality in Saint John County, New Brunswick, 2006-2016

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BACKGROUND:

According to the Institution for Safe Medication Practices in Canada, psychotherapeutic medications (e.g. benzodiazepines, antidepressants, neuroleptics) are the second most common class of drugs, outranked only by opiates, in medication incidents leading to death in Canada. [1] Among opioid poisonings leading to emergency room visits and/or hospitalization, benzodiazepine (BZD) was the most common co-occurring drug class and was found in 19% of these hospitalizations.[2] One study noted that the presence of benzodiazepines was associated with a 1.6 times greater risk (95% CI 1.1-2.5) of opioid related death in individuals on methadone maintenance therapy after controlling for a number of other factors including the use of other opioids/medications, age and sex.[3] Despite the evidence discouraging the co-administration of benzodiazepines and opioids, this practice continues to be quite common with a prevalence estimated in chronic opioid users of 46%.[4]

METHODS:

A retrospective review of all accidental, intentional and undetermined illicit drug toxicity deaths which occurred between January 1, 2006 and December 31, 2016 was conducted in collaboration with the Coroner Services department in New Brunswick using final coroner reports issued on each death. A drug toxicity death was classified as illicit if it involved any drug produced, trafficked and/or consumed illicitly or in excess of prescribed quantities including opioids (e.g. morphine, heroin, methadone, fentanyl), other central nervous system depressants (e.g. barbiturates, nonbarbiturate depressants, BZD), central nervous system stimulants (e.g. cocaine, crack cocaine, amphetamines), and hallucinogens (e.g. LSD, PCP). Overdose deaths were included if they were classified as both polydrug and accidental toxicity deaths. Deaths were then classified into 3 categories based on toxicology results: (1) one or more opioids, (2) one or more opioids and one or more benzodiazepines, or (3) methadone as the only opioid present and BZD. Rates of drug toxicity deaths per 100,000 population were calculated using the most recent Statistics Canada Census population estimates for each year. Data were stratified between all of New Brunswick (NB) and Saint John County (SJC) alone to identify any key differences in characteristics and trends.

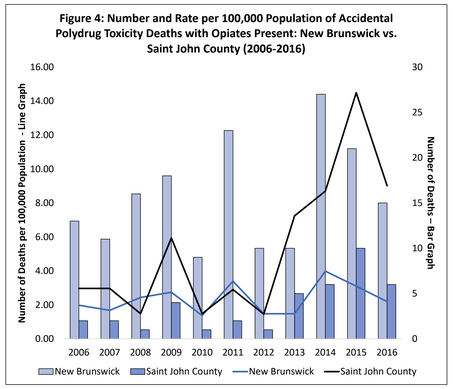

Figure 4: Number and Rate per 100,000 Population of Accidental Polydrug Toxicity Deaths with Opiates Present: New Brunswick vs. Saint John County (2006-2016)

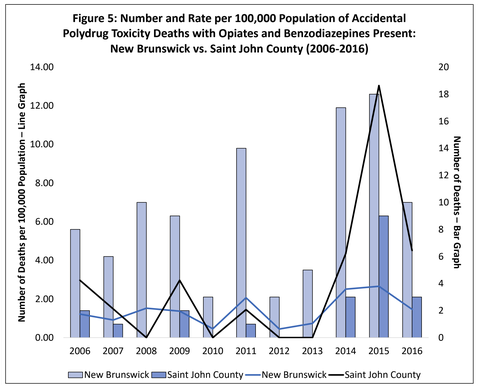

Figure 5: Number and Rate per 100,000 Population of Accidental Polydrug Toxicity Deaths with Opiates and Benzodiazepines Present: New Brunswick vs. Saint John County (2006-2016)

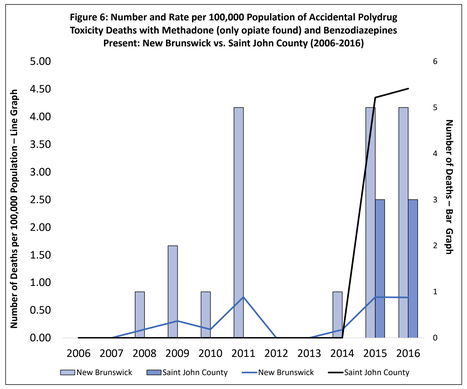

Figure 6: Number and Rate per 100,000 Population of Accidental Polydrug Toxicity Deaths with Methadone (only opiate found) and Benzodiazepines Present: New Brunswick vs. Saint John County (2006-2016)

Table 1: Proportion of Accidental Polydrug Toxicity Deaths in Each Category in New Brunswick and Saint John County

	NB	SJC
Polydrug w/ Opioids	75%	72%
Polydrug w/ Opioids & BZD	45%	45%
Polydrug w/ BZD & Methadone (+/- other opioids)	14%	19%
Polydrug w/ BZD & Methadone (only opioid present)	9%	13%

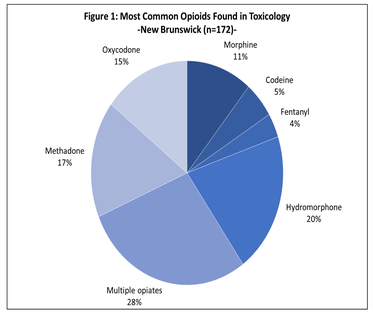

Figure 1: Most Common Opioids Found in Toxicology -New Brunswick (n=172)-

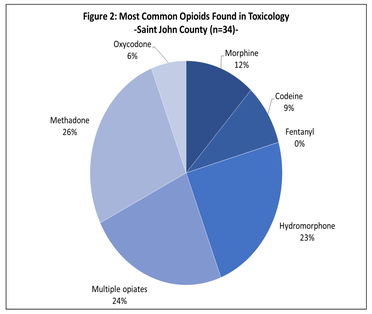

Figure 2: Most Common Opioids Found in Toxicology -Saint John County (n=34)-

Table 2: Baseline Characteristics of Polydrug Overdose Deaths Overall and By Co-Occurrence of Opiates and/or Benzodiazepines

	Polydrug		Polydrug w/ Opiates		Polydrug w/ Opiates and BZD		Polydrug w/ Methadone and BZD	
	N.B. (n=231)	SJC (n=47)	N.B. (n=173)	SJC (n=34)	N.B. (n=103)	SJC (n=21)	N.B. (n=20)	SJC (n=6)
Mean age	44.0	44.3	42.7	42.5	42.8	45.3	37.6	42.7
% Male	60.9%	55.3%	59.9%	41.2%	55.9%	33.3%	60.0%	33.3%
% Out of hospital death	75.3%	78.7%	76.3%	82.4%	75.7%	81.0%	75.0%	83.3%
History of alcohol abuse	24.4%	17.4%	21.1%	12.1%	20.8%	10.0%	11.8%	16.7%
History of overdose	5.5%	2.2%	5.6%	3.0%	5.2%	5.0%	5.9%	16.7%
History of depression	33.3%	23.4%	30.6%	17.7%	30.1%	28.6%	35.0%	50.0%
History of chronic pain	23.0%	27.7%	25.6%	35.3%	29.4%	47.6%	20.0%	50.0%
Prescriptions at time of death*:	**N.B. (n=154)**	**SJC (n=31)**	**N.B. (n=115)**	**SJC (n=24)**	**N.B. (n=68)**	**SJC (n=13)**	**N.B. (n=12)**	**SJC (n=4)**
Benzodiazepines	59.7%	45.2%	60.90%	45.80%	67.7%	61.5%	75.0%	50.0%
Opioids (not methadone)	38.9%	35.5%	47.0%	37.5%	50.0%	46.2%	0.0%	0.0%
Methadone	5.8%	9.7%	7.6%	12.5%	10.1%	23.1%	53.9%	75.0%
Sleep Aid (Zopiclone/Trazodone)	19.5%	25.8%	20.8%	29.1%	23.5%	30.8%	41.7%	75.0%

*Note that prescription information at the time of death was only available in approximately 65% of deaths. Caution should be used in interpreting results in the context of non-prescribed drug toxicity deaths.

RESULTS:

Of 516 illicit drug toxicity deaths which occurred between 2006 and 2016, 231 (44.8%) were classified as accidental and polydrug deaths. SJC, which has on average 10.2% (~ 68,000 pop.) of the New Brunswick population, accounted for 20.3% of those 231 deaths (n=47). As seen in Table 1, 72-75% of these deaths had opiates present on toxicology. In NB, a combination of 2 or more opiates on toxicology was the most common finding (Figure 1), while in SJC, methadone appeared in the highest proportion of deaths (Figure 2). Co-occurrence of benzodiazepines and opiates in toxicology was found in 45% of all polydrug accidental toxicity deaths in both NB and SJC. Based on available information regarding valid prescriptions at the time of death, only about 68% of NB BZD and opioid toxicity and 62% of SJC BZD and opioid toxicity deaths had prescriptions for BZD at the time of their deaths (Table 2). As also noted in Table 2, SJC toxicity deaths in all categories had higher proportions of out-of-hospital deaths and documentation in coroner's reports of chronic pain and depression. SJC also had a much higher proportion of female deaths than seen provincially. The proportion of female deaths increased across categories from 5.6% higher than the NB proportion in accidental polydrug toxicity deaths to 26.7% higher in deaths involving methadone as the only opiate together with benzodiazepines. Figure 3 demonstrates other drugs found on toxicology among individuals with both BZD and opioids present.

As shown in Figure 4, the rate of accidental polydrug toxicity deaths involving opiates per 100,000 population in SJC has been consistently higher than the provincial rate since 2013. Of the 73 deaths from 2013-2016, 37% (n=27) have occurred in SJC. Among opioid and benzodiazepine toxicity deaths, rates 1.7 to 4.9 times higher than the province have been seen in SJC which has 33% of the total number of deaths in this category (Figure 5). During the study period, no deaths involving methadone as the only opiate found with benzodiazepines had been recorded in SJC prior to 2015. In 2015-2016, SJC had 60% of all deaths with this combination with rates 6 times higher than the province as a whole (Figure 6). Closer examination of the deaths involving methadone and BZD in combination demonstrated that clonazepam was the most common BZD found in toxicology. While only about 65% of these deaths had prescription information available, it is noted that in NB as a whole only 58% (7/12) who were prescribed benzodiazepines had the same benzodiazepines in toxicology while only 50% had a prescription for methadone. In SJC only 25% (1/4) had the same benzodiazepines found as prescribed on toxicology and only similarly only 50% had prescriptions for methadone.

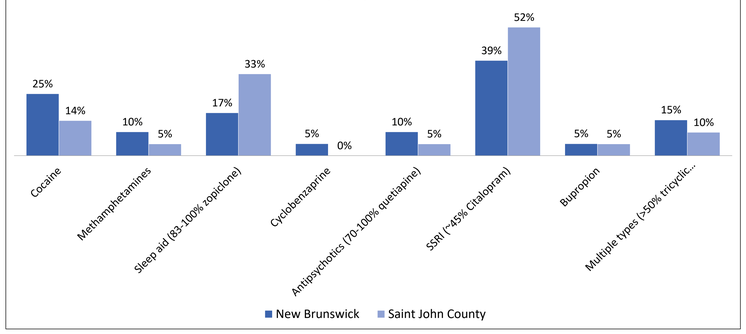

Figure 3: Drugs found in toxicology among drug toxicity deaths with both opioids and benzodiazepines present (2006-2016)

CONCLUSIONS:

These results show that, despite the well documented increased risk of serious adverse events and death when opioids and benzodiazepines are combined, their co-administration appears to be common both in New Brunswick and Saint John County. In 2016, the United States Food and Drug Administration required boxed warnings to be added to approximately 400 opioid or benzodiazepine products citing serious risks including respiratory depression, coma and death from their combined use.[5] In this study, almost half of all accidental polydrug toxicity deaths which occurred had both benzodiazepines and opioids present. From the available information on prescribed medications at the time of death, over 60% of these patients had valid prescriptions for both classes of medication suggesting a need to further educate regarding the importance of avoiding their co-prescription unless absolutely necessary, particularly for those with addiction issues due to the high abuse potential of both drugs. Of particular concern from the results of this review is the sudden spike in opioid and benzodiazepine accidental drug toxicity deaths in Saint John County in 2015-2016 especially given that available prescription history indicates that half or more appear to have acquired the medications illicitly. High rates of diverted prescription drugs associated with abuse and fatal toxicity is a significant concern in Saint John County as well as throughout the province. Caution is warranted when prescribing opioids, including methadone, with benzodiazepines and clinicians should be prudent even when prescribing benzodiazepines and opioids in isolation.

References:

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2. Canadian Institute for Health Information. "Hospitalizations and Emergency Department Visits Due to Opioid Poisoning in Canada. https://secure.cihi.ca/free_products/Opioid%20Poisoning%20Report%20%20EN.pdf Accessed November 22, 2017.
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5. Food and Drug Administration. "FDA requires strong warnings for opioid analgesics, prescription opioid cough products, and benzodiazepine labeling related to serious risks and death from combined use." Press Release: August 31, 2016.