JKMS

Original Article
Oncology & Hematology

Check for updates

Survey of Opioid Risk Tool Among Cancer Patients Receiving Opioid Analgesics

So Yeon Oh (iD),[1] **Kwonoh Park** (iD),[1] **Su-Jin Koh** (iD),[2] **Jung Hun Kang** (iD),[3] **Myung Hee Chang** (iD),[4] and **Kyung Hee Lee** (iD) [5]

[1]Medical Oncology and Hematology, Department of Internal Medicine, Pusan National University Yangsan Hospital, Yangsan, Korea
[2]Department of Hematology and Oncology, Ulsan University Hospital, Ulsan University College of Medicine, Ulsan, Korea
[3]Hematology and Oncology, Department of Internal medicine, Gyeongsang National University College of Medicine, Jinju, Korea
[4]Oncology and Hematology, Department of Internal Medicine, National Health Insurance Service Ilsan Hospital, Goyang, Korea
[5]Hematology and Oncology, Department of Internal Medicine, Yeungnam University College of Medicine, Daegu, Korea

OPEN ACCESS

Address for Correspondence:
Kyung Hee Lee, MD, PhD
Division of Oncology-Hematology, Department of Internal Medicine, Yeungnam University College of Medicine, 170 Hyeonchung-ro, Nam-gu, Daegu 42415, Republic of Korea.
Email: lkhee@med.yu.ac.kr

ORCID iDs
So Yeon Oh (iD)
https://orcid.org/0000-0002-2562-9257
Kwonoh Park (iD)
https://orcid.org/0000-0002-7404-1257
Su-Jin Koh (iD)
https://orcid.org/0000-0002-1545-8036
Jung Hun Kang (iD)
https://orcid.org/0000-0001-5013-2683
Myung Hee Chang (iD)
https://orcid.org/0000-0002-2426-7514

ABSTRACT

Background: The risk of opioid-related aberrant behavior (OAB) in Korean cancer patients has not been previously evaluated. The purpose of this study is to investigate the Opioid Risk Tool (ORT) in Korean cancer patients receiving opioid treatment.

Methods: Data were obtained from a multicenter, cross-sectional, nationwide observational study regarding breakthrough cancer pain. The study was conducted in 33 South Korean institutions from March 2016 to December 2017. Patients were eligible if they had cancer-related pain within the past 7 days, which was treated with strong opioids in the previous 7 days.

Results: We analyzed ORT results of 946 patients. Only one patient in each sex (0.2%) was classified as high risk for OAB. Moderate risk was observed in 18 males (3.3%) and in three females (0.7%). Scores above 0 were primarily derived from positive responses for personal or familial history of alcohol abuse (in men), or depression (in women). In patients with an ORT score of 1 or higher (n = 132, 14%), the score primarily represented positive responses for personal history of depression (in females), personal or family history of alcohol abuse (in males), or 16–45 years age range. These patients had more severe worst and average pain intensity (proportion of numeric rating scale ≥ 4: 20.5% vs. 11.4%, $P < 0.001$) and used rescue analgesics more frequently than patients with ORT scores of 0. The proportion of moderate- or high-risk patients according to ORT was lower in patients receiving low doses of long-acting opioids than in those receiving high doses (2.0% vs. 6.6%, $P = 0.031$). Moderate or high risk was more frequent when ORT was completed in an isolated room than in an open, busy place (2.7% vs. 0.6%, $P = 0.089$).

Conclusions: The score of ORT was very low in cancer patients receiving strong opioids for analgesia. Higher pain intensity may associate with positive response to one or more ORT item.

Keywords: Opioid Risk Tool; Opioid-Related Disorders; Narcotic-Related Disorders; Cancer Pain

Generated by xmlinkpress

JKMS

Kyung Hee Lee
https://orcid.org/0000-0003-0462-2512

INTRODUCTION

Opioid analgesics are the most important drugs for controlling cancer pain. Nevertheless, their potential for dependency, misuse, and addiction has long been a major concern. Recently, the prescription of opioids has soared worldwide. Because of cultural conventions, opioid usage has been traditionally low in East Asia, but it has increased rapidly in recent years.[1,2] In a large-scale cohort study, the proportion of opioid users in South Korea increased six to nine times from 2002 to 2015.[3] Moreover, opioid-related chemical coping was 21% among South Korean patients receiving long-term opioid therapy for chronic non-cancer pain in a cross-sectional study.[4] Thus, concerns about opioid-related aberrant behavior (OAB) are now greater than ever.

The rate of opioid misuse is approximately 21% to 29% among patients with chronic pain, according to a systematic review of studies conducted in North America and Europe.[5] To prescreen high-risk patients, many tools have been developed for predicting the risk of OAB.[6] The Opioid Risk Tool (ORT), Current Opioid Misuse Measure (COMM), and Patient Medication Questionnaire (PMQ) are common risk assessment tools.[7-9] Although no controlled study has directly compared the performance of these tools, ORT is the most widely used. In the original study describing the use of ORT, approximately 66% and 24% of patients with chronic pain were classified as having a moderate and high risk of aberrant opioid use, respectively. With respect to cancer patients, the risk of OAB varies considerably according to cancer type and treatment situation. Moderate to high risk of OAB predicted by ORT has been reported in approximately 15% to 43% of cancer patients.[10-12] In a recent study using different screening tools, 10% to 39% of cancer patients receiving supportive care were noted to be at risk of OAB.[13,14]

In this paper, we describe the ORT results of a large multicenter, nationwide survey regarding breakthrough cancer pain in South Korean patients. The results of the entire study population will be published elsewhere.[15] In this study, we used ORT to evaluate the risk of OAB in patients receiving opioids to control cancer pain.

METHODS

Study design

This study is a subgroup analysis of a multicenter, cross-sectional, nationwide observational study about breakthrough cancer pain. The study was conducted in 33 South Korean institutions from March 2016 to December 2017. The full analysis set of the original study includes 956 subjects which will be published elsewhere. This paper reports the results of subjects who completed the ORT from the original study.

Patient eligibility

Patients were eligible if they met the following criteria: 1) aged 19 years or older, 2) histologically-diagnosed cancer, 3) current or previous anti-cancer treatment (surgery, radiation, or systemic therapy) or palliative care, 4) cancer-related pain within 7 days before the date of written informed consent, 5) use of strong opioids within 7 days before the date of written informed consent, and 6) cognitive function sufficient to read and understand the informed consent form and study questionnaires.

Data acquisition

We first collected details about cancer status and treatment history from the medical records of patients who provided written informed consent. Patients were requested to complete a questionnaire of ORT which was written in Korean (**Supplementary Data 1**). If patients were unable to complete the questionnaires on their own, their caregiver was permitted to record the responses. In the absence of a caregiver, the clinical research coordinator recorded the responses. The identity of the person providing assistance was recorded, as was the physical location where the questionnaires were completed. The ORT scores of 0–3 (low risk), 4–7 (moderate risk), or ≥ 8 (high risk), indicated the probability of OABs according to the original study.[7]

Statistical analyses

Continuous variables are summarized as mean ± standard deviation (SD) or median (minimum, maximum). Frequency, percentage, and cumulative percentage are presented for categorical variables. To compare two continuous variables, the two-sample t-test was used for normally distributed data, and the Mann-Whitney U test was used for non-normally distributed variables. Chi-square test or Fisher's exact test was used to compare categorical variables between groups. All statistical analyses were performed using IBM SPSS Statistics version 26 and Microsoft Excel 2019.

Ethical statement

The authors are accountable for all aspects of this work. All authors are ensuring that questions related to the accuracy or integrity of the work are appropriately investigated and resolved. The protocol was performed in accordance with the principles of the Declaration of Helsinki (as revised in 2013) and the Good Clinical Practice Guidelines defined by the International Conference on Harmonization. After receiving approval from the KCSG Protocol Review Committee, this study was also approved by the Institutional Review Boards (IRBs) of each participating center (Pusan National University Yangsan Hospital IRB No. 04-2016-002). All patients provided written informed consent before enrollment.

RESULTS

Patient characteristics

Total 946 patients completed the ORT. The characteristics of patients are summarized in **Table 1**. The majority of patients had stage IV cancer and a fair performance status, and most had received anti-cancer treatment within the previous 4 weeks.

ORT results

The ORT results are presented in **Table 2**. In men, scores above 0 were primarily derived from positive responses for depression, personal or familial history of alcohol abuse, and age within the 16 to 45 years range. In women, the majority of scores above 0 were derived from positive responses for depression and the 16 to 45 years age range. Drug abuse and a history of preadolescent sexual abuse or psychological disease other than depression were extremely rare in both sexes. **Fig. 1** is a color-coded depiction of the number of positive responses for each ORT item as an easy-to-read presentation of the results. The mean total ORT score was very low in both men and women, with a median value of 0 in both sexes. The distribution of total scores for each sex is presented in **Table 3**. Most males were classified as low risk, and 18 (3.3%) were considered moderate risk. Likewise, most females were classified as low

Table 1. Patient characteristics

Characteristics	Values (N = 946)
Age, yr	63 (27, 91)
Sex	
Male	537 (56.8)
Female	409 (43.2)
Time from initial diagnosis, mon	15 (0, 384)
Relapse	
No	625 (66.1)
Yes, relapsed	312 (33.0)
Unknown	9 (1.0)
Time to relapse, mon (n = 312)	12 (0, 164)
Primary cancer diagnosis	
Colorectal	125 (13.2)
Lung	110 (11.6)
Breast	107 (11.3)
Stomach	100 (10.6)
Pancreas	91 (9.6)
Other	413 (43.6)
Stage	
1	10 (1.1)
2	31 (3.3)
3	74 (7.8)
4	798 (84.4)
Unknown	33 (3.5)
ECOG PS	
0	60 (6.3)
1	598 (63.2)
2	188 (19.9)
3	58 (6.1)
4	18 (1.9)
Unknown	24 (2.5)
Recent anti-cancer treatment (past 4 wk)	
Yes	658 (69.6)
No	288 (30.4)
Type of recent anti-cancer treatment (n = 658)	
Chemotherapy	632 (88.4)[a]
Adjuvant	33 (5.2)
Neoadjuvant	9 (1.4)
Palliative	584 (92.4)
Unknown	6 (0.9)
Radiotherapy	77 (10.8)
Surgery	6 (0.8)

Values are number (percentage) or median (minimum, maximum).
ECOG = Eastern Cooperative Oncology Group, PS = performance status.
[a]Overlap was permitted.

risk, and only three (0.7%) were classified as moderate risk. Only one subject (0.2%) in each sex was considered high risk according to ORT. The proportion of moderate- or high-risk patients was higher in men than in women (3.5% vs. 1.0%, $P = 0.011$ by Fisher's exact test).

ORT scores and pain intensity

Because the vast majority of subjects had a 0 ORT score, we further analyzed the patients who answered 'YES' on any item of the ORT (n = 132, 14%). These patients had a higher average pain intensity score during the past week than those with a 0 ORT score (mean ± SD: 4.04 ± 2.10 vs. 3.22 ± 1.94, $P < 0.001$ by t-test). Furthermore, patients with moderate or severe pain according to the average 1-week pain intensity score were more likely to answer 'YES' to at least one ORT item than those with weak pain intensity (20.5% vs. 11.4%, $P < 0.001$ by

Table 2. Opioid Risk Tool results according to sex

ORT items and total scores	Male (n = 537)	Female (n = 409)
Family history of substance abuse		
Alcohol		
No	521 (97)	401 (98)
Yes	16 (3)	8 (2)
Illegal drugs		
No	537 (100)	409 (100)
Yes	0 (0)	0 (0)
Prescription drugs		
No	531 (98.9)	408 (99.8)
Yes	6 (1.1)	1 (0.2)
Personal history of substance abuse		
Alcohol		
No	518 (96.5)	406 (99.3)
Yes	19 (3.5)	3 (0.7)
Illegal drugs		
No	535 (99.8)	409 (100)
Yes	1 (0.2)	0 (0)
Prescription drugs		
No	535 (99.6)	408 (99.8)
Yes	2 (0.4)	1 (0.2)
Age (16–45 yr)		
Not 16–45	522 (97.2)	385 (94.1)
16–45	15 (2.8)	24 (5.9)
History of preadolescent sexual abuse		
No	537 (100)	408 (99.8)
Yes	0 (0)	1 (0.2)
Psychological disease		
Attention deficit, obsessive-compulsive disorder, bipolar, schizophrenia		
No	533 (99.3)	408 (99.8)
Yes	4 (0.7)	1 (0.2)
Depression		
No	519 (96.6)	371 (90.7)
Yes	18 (3.4)	38 (9.3)
Total score		
Mean ± SD	0.3 ± 1.2	0.2 ± 0.7
Median (minimum, maximum)	0 (0, 12)	0 (0, 8)

Data for ORT items are numbers (percentage).
NA = not available, ORT = Opioid Risk Tool, SD = standard deviation.

No. of 'YES'	Male	Female
Age (16–45 yr)	15	24
F.Hx: alcohol	16	8
F.Hx: illegal drugs	0	0
F.Hx: prescription drugs	6	1
Hx: alcohol	19	3
Hx: illegal drugs	1	0
Hx: prescription drugs	2	1
Hx: sexual abuse	0	1
Psychological disorders	4	1
Depression	18	38

Fig. 1. The number of patients who answered 'YES' to each Opioid Risk Tool item are displayed in a different color according to the size of number. The higher the number, the darker the color.
F.Hx = family history, Hx = personal history.

Table 3. Distribution of ORT total scores according to sex

Total ORT score	Male	Female
0	475 (88.5)	339 (82.9)
1	22 (4.1)	61 (14.9)
2	1 (0.2)	3 (0.7)
3	20 (3.7)	2 (0.5)
4	9 (1.7)	3 (0.7)
5	3 (0.6)	0
6	5 (0.9)	0
7	1 (0.2)	0
8	0	1 (0.2)
12	1 (0.2)	0
Sum	537 (100)	409 (100)

Values are presented as number (%).
NA = not available, ORT = Opioid Risk Tool.

chi-squared test) (**Table 4**). Likewise, patients with an ORT score of 1 or more had a higher maximal pain intensity during the previous 1 week than those with a 0 ORT score (mean ± SD: 6.66 ± 2.53 vs. 6.00 ± 2.47, $P = 0.013$ by t-test). Patients with an ORT score of at least 1 also used short-acting opioids more frequently to control breakthrough pain, compared to patients with an ORT score of 0 (2.5 ± 1.6 times/day vs. 2.0 ± 1.6 times/day, $P = 0.013$ by t-test). Additionally, pain interfered with the enjoyment of life in the past 24 hours more in patients with an ORT of least 1 than in those with an ORT score of 0 (Brief Pain Inventory-Short Form, Korean version, scores: 6.7 ± 2.9 vs. 6.1 ± 2.9, $P = 0.037$ by t-test).

Opioid utilization and ORT score

The daily dose of total long-acting opioids was converted to oral morphine equivalents (OME) for each patient. The mean and median OMEs were 93.1 ± 246.8 mg and 60 mg (0, 6,300), respectively. The mean daily OME of patients classified as moderate or high risk according to ORT was not statistically significantly higher than that of the low-risk patients (mean ± SD: 143.1 ± 194.6 mg vs. 91.9 ± 247.9 mg, $P = 0.228$ by t-test). However, the proportion of patients who were classified as moderate or high risk was lower in the low-dose group than in the high-dose group (2.1% vs. 6.6%, $P = 0.031$ by Fisher's exact test) (**Table 5**).

Table 4. Association between average pain intensity in the previous week and ORT scores

ORT score[a]	Average pain intensity		Sum	P value[b]
	Weak	Moderate or severe		
0	601 (64)	213 (23)	814 (86)	< 0.001
≥ 1	77 (8)	55 (6)	132 (14)	
Sum	678 (72)	268 (28)	946 (100)	

Values are presented as number (%).
ORT = Opioid Risk Tool.
[a]Based on the number of ORT items with a 'YES' answer, excluding the age range item; [b]χ^2 test.

Table 5. Association between ORT risk classification and dose of long-acting opioids for background pain

Dose of long-acting opioids[a]	ORT risk		Sum	P value[b]
	Low	Moderate or high		
Low	852	18	870	0.031
High	71	5	76	
Sum	923	23	946	

ORT = Opioid Risk Tool.
[a]Total daily dose of long-acting opioids (i.e., extended-release, controlled-release, and slow-release forms) for background pain converted to oral morphine equivalents. High dose was defined as daily OME of 200 mg or higher; [b]Fisher's exact test.

Circumstances during ORT completion

We further investigated whether the circumstances when completing ORT affected the ORT results. First, we compared the scores of self-completed ORT (n = 420) with the scores of ORTs completed with the assistance of a caregiver (n = 56) or study staff (n = 471). Although all high-risk patients were in the self-completed group, there was no statistically significant difference in ORT scores according to whether the ORT was completed alone or with assistance (P = 0.111, Likelihood ratio Chi-Square). Second, we tested whether the environment where patients completed the ORT correlated with ORT scores. ORT scores tended to be lower when ORT was completed in an open, busy space (n = 154) than when it was completed in a quiet, isolated room (n = 792) (moderate or high risk in open, busy location vs. quiet, isolated location: 0.6% vs. 2.7%, P = 0.089 by Fisher's exact test, **Supplementary Table 1**).

DISCUSSION

In this study, we investigated the risk of OAB by using ORT to survey cancer patients who were already receiving strong opioids for pain control. To our knowledge, this is the first study to investigate ORT results in Korean patients with cancer. In this study, the score of ORT was very low in cancer patients receiving strong opioids for cancer-related pain. Moderate risk was observed rare; in 18 males (3.3%) and in three females (0.7%). Among almost 1,000 patients, only one man and one woman were classified as high risk. This proportion (0.2%) was lower than the percentages previously reported in the literature. Nearly 89% of males and 83% of females had ORT scores of 0. Of those patients with an ORT score of 1 or higher, the score primarily reflected positive responses for a history of depression, alcohol abuse, and age with the 16 to 45 years range.

In this study, we demonstrated several new findings. Patients with an ORT score of 1 or more had higher average and worst pain intensities, reported more interference with their enjoyment of life because of pain, and used more short-acting opioids for breakthrough pain, when compared to patients with an ORT score of 0. Additionally, high-dose opioid users tended to be classified as moderate or high risk according to ORT more frequently than low-dose opioid users. We also noted that the place where ORT is completed may influence the results. Patients were more frequently classified as moderate or high risk when ORT was completed in a quiet, independent environment than when it was compared in a busy, open space. This result suggests that if researchers use ORT in a future study, it should be completed in a quiet, independent location.

Although ORT scores seemed be associated with pain intensity, it is not clear that patients with more severe pain have a higher risk of OAB. However, the likelihood that patients with a higher risk for OAB may demand more opioids cannot be ruled out. Conversely, consideration should be given to the possibility that positive response on some of the ORT items may reflect a lower pain threshold. Many studies have reported substantial genetic influences in drug addiction, reflecting the hereditability of addiction.[16-18] This genetic trait may influence both ORT scores and opioid demands. We can assume that genetic predisposition of drug addiction may have association with lowered pain threshold. Some studies already suggested that pain threshold may vary among individuals by genetic predisposition.[19] Few candidate genes (such as COMT, OPRM1, GCH1, TRPV1, or OPRD1), haplotypes or single nucleotide polymorphisms are investigated as contributing traits.[20-24]

Because this study was cross-sectional, we cannot check causality and should interpret this finding with caution. However, we believe that these findings could provide hints for future studies.

It is worth considering why our population had an overall low score of ORT. One possibility is that the actual risk is low in patients with cancer pain. In the past, it was generally accepted that cancer patients had an extremely low likelihood of opioid addiction or OAB.[25-27] However, more recent studies have reported that the rate of opioid addiction or aberrant behavior is increasing in this patient population. The prevalence of OAB was reported as low as 7.7% and as high as 43% in these more recent studies.[10-14,28] Therefore, it is necessary to consider the possibility that the risk of OAB in cancer patients is higher than previously known. Another possible explanation for the overall low risk observed in the current study was that patients may have wanted to be perceived as a 'good patient' by their doctors.[29,30] Consequently, they may have concealed elements of their past history that they thought would have little effect, or even a negative impact, on their treatment. Although statistical significance was not achieved, no one was classified as high risk when ORT was completed with the assistance of medical staff. All high-risk patients were in the group of patients who completed ORT by themselves. A third, and most important, possibility is that ORT is not a suitable risk predicting tool in cancer patients who are already receiving opioid analgesics. ORT was originally developed to predict the probability of aberrant behaviors indicative of abuse in patients with chronic pain.[7] The original study presented no information about the primary diagnosis of the subjects. In cancer patients, the risk of OAB has been reported to vary considerably, from 10% to 40%.[10-14] In a study comparing ORT of cancer patients and heart failure patients, the proportion of moderate- to high-risk patients was higher in cancer patients (39% versus 23%), although the difference was not statistically significant.[31] Some studies have reported that the predictive performance of ORT is relatively poor in various populations of patients with chronic non-cancer pain. The ORT scores of chronic non-cancer pain patients using a physician-administered ORT in a tertiary care pain clinic were quite different from those reported in the original ORT study.[32] In another study of patients with chronic pain, neither patient-generated nor physician-generated ORT was predictive of moderate-to-severe aberrant drug-related behavior.[33] Thus, ORT may not be an appropriate predictor for OAB, and some investigators have tried to simplify and improve the performance of this risk assessment tool.[34] A final consideration is whether selection bias occurred in this study. This study enrolled subjects of various carcinomas with very simple inclusion/exclusion criteria. In fact, most cancer patients who were prescribed opioids within one week for cancer pain were able to participate. In a nationwide study of 2003 Korean cancer patients, opioids were administered in 65% of patients with cancer pain.[35] Whereas, only patients who were prescribed opioids were enrolled in this study, so it is possible that subjects with relatively more severe pain were included in this study. However, in terms of the prescribed opioids dose, the OME dose was 93 mg (mean, median is 60 mg) per day, which is not significantly different from the daily doses of an average of between 100 mg and 250 mg in a systematic review.[36] In a Korean study, though it was hydromorphone, the mean daily OME dose was 53mg among a similarly advanced cancer patient population.[37] Therefore, the probability of selection bias seems to be low.

This study has several limitations, First, this study was not specifically designed to evaluate OAB; instead, ORT was completed as part of a study regarding cancer pain. Thus, because the study's endpoint was not targeted for ORT, one must be careful about drawing conclusions regarding OAB in cancer patients. As discussed above, another screening tool for OAB may have performed better in this patient population, which could be explored in future studies.

Second, the cancer stage was heterogenous in our study population. At least 115 patients (12%) were at stage I to III, indicating that they may have had no residual tumor. Opioid prescribing may differ substantially between patients with and without viable tumor tissue. Third, ORT was completed under varying circumstances, according to the study timeline and study sites, and environment and location may affect ORT results. For example, ORT contains personal information, which may be embarrassing to patients. Therefore, it is probably more appropriate to complete this survey in an isolated space.

In summary, the score of ORT was very low in Korean cancer patients receiving strong opioids for pain control. Patients with at least one ORT risk item (ORT score of 1 or higher) had higher average and worse pain intensities, reported more interference with enjoyment of life because of pain, and used short-acting opioids more frequently. The circumstances under which ORT was completed may have influenced the results. In future studies evaluating the risk of OAB, it is recommended that risk predicting tools be selected according to the subjects' characteristics.

ACKNOWLEDGMENTS

SUPPLEMENTARY MATERIALS

Supplementary Data 1
The Korean form of Opioid Risk Tool.

Click here to view

Supplementary Data 2
A complete list of participating sites and staffs.

Click here to view

Supplementary Table 1
The relationship of place where ORT was surveyed and the score of ORT

Click here to view

REFERENCES

1. Choi AG, Ko JH, Kim JS, Son ES, Kwon KH. Recent statistics and risk factors of fentanyl buccal tablet related opioid dependence tendency at a tertiary hospital in Korea. *J Korean Soc Health Syst Pharm* 2019;36(4):476-85.
   CROSSREF
2. World Health Organization. *Atlas on Substance Use (2010): Resources for the Prevention and Treatment of Substance Use Disorders*. Geneva, Switzerland: World Health Organization; 2009.

3. Oh TK, Jeon YT, Choi JW. Trends in chronic opioid use and association with five-year survival in South Korea: a population-based cohort study. *Br J Anaesth* 2019;123(5):655-63.
   PUBMED | CROSSREF

4. Castañeda AM, Lee CS, Kim YC, Lee D, Moon JY. Addressing opioid-related chemical coping in long-term opioid therapy for chronic noncancer pain: a multicenter, observational, cross-sectional Study. *J Clin Med* 2018;7(10):354.
   PUBMED | CROSSREF

5. Vowles KE, McEntee ML, Julnes PS, Frohe T, Ney JP, van der Goes DN. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. *Pain* 2015;156(4):569-76.
   PUBMED | CROSSREF

6. Ducharme J, Moore S. Opioid use disorder assessment tools and drug screening. *Mo Med* 2019;116(4):318-24.
   PUBMED

7. Webster LR, Webster RM. Predicting aberrant behaviors in opioid-treated patients: preliminary validation of the Opioid Risk Tool. *Pain Med* 2005;6(6):432-42.
   PUBMED | CROSSREF

8. Butler SF, Budman SH, Fernandez KC, Houle B, Benoit C, Katz N, et al. Development and validation of the current opioid misuse measure. *Pain* 2007;130(1-2):144-56.
   PUBMED | CROSSREF

9. Adams LL, Gatchel RJ, Robinson RC, Polatin P, Gajraj N, Deschner M, et al. Development of a self-report screening instrument for assessing potential opioid medication misuse in chronic pain patients. *J Pain Symptom Manage* 2004;27(5):440-59.
   PUBMED | CROSSREF

10. Barclay JS, Owens JE, Blackhall LJ. Screening for substance abuse risk in cancer patients using the Opioid Risk Tool and urine drug screen. *Support Care Cancer* 2014;22(7):1883-8.
    PUBMED | CROSSREF

11. Garcia C, Lefkowits C, Pelkofski E, Blackhall L, Duska LR. Prospective screening with the validated Opioid Risk Tool demonstrates gynecologic oncology patients are at low risk for opioid misuse. *Gynecol Oncol* 2017;147(2):456-9.
    PUBMED | CROSSREF

12. Ma JD, Horton JM, Hwang M, Atayee RS, Roeland EJ. A single-center, retrospective analysis evaluating the utilization of the opioid risk tool in opioid-treated cancer patients. *J Pain Palliat Care Pharmacother* 2014;28(1):4-9.
    PUBMED | CROSSREF

13. Yennurajalingam S, Edwards T, Arthur JA, Lu Z, Najera J, Nguyen K, et al. Predicting the risk for aberrant opioid use behavior in patients receiving outpatient supportive care consultation at a comprehensive cancer center. *Cancer* 2018;124(19):3942-9.
    PUBMED | CROSSREF

14. Yasin JT, Leader AE, Petok A, Garber G, Stephens B, Worster B. Validity of the screener and opioid assessment for patients with pain-revised (SOAPP-R) in patients with cancer. *J Opioid Manag* 2019;15(4):272-4.
    PUBMED | CROSSREF

15. Koh SL, Oh S, Kang J, Koo D, Yun S, Chang M, et al. Abstracts for MASCC/ISOO Annual Meeting 2019. In: Supportive Care in Cancer; 2019 2019/06/01; San Francisco, CA; p. 1-302.

16. Kendler KS, Jacobson KC, Prescott CA, Neale MC. Specificity of genetic and environmental risk factors for use and abuse/dependence of cannabis, cocaine, hallucinogens, sedatives, stimulants, and opiates in male twins. *Am J Psychiatry* 2003;160(4):687-95.
    PUBMED | CROSSREF

17. Wang SC, Chen YC, Lee CH, Cheng CM. Opioid addiction, genetic susceptibility, and medical treatments: a review. *Int J Mol Sci* 2019;20(17):4294.
    PUBMED | CROSSREF

18. Tsuang MT, Lyons MJ, Meyer JM, Doyle T, Eisen SA, Goldberg J, et al. Co-occurrence of abuse of different drugs in men: the role of drug-specific and shared vulnerabilities. *Arch Gen Psychiatry* 1998;55(11):967-72.
    PUBMED | CROSSREF

19. Fillingim RB, Wallace MR, Herbstman DM, Ribeiro-Dasilva M, Staud R. Genetic contributions to pain: a review of findings in humans. *Oral Dis* 2008;14(8):673-82.
    PUBMED | CROSSREF

20. Diatchenko L, Anderson AD, Slade GD, Fillingim RB, Shabalina SA, Higgins TJ, et al. Three major haplotypes of the β2 adrenergic receptor define psychological profile, blood pressure, and the risk for development of a common musculoskeletal pain disorder. *Am J Med Genet B Neuropsychiatr Genet* 2006;141B(5):449-62.
    PUBMED | CROSSREF

21. Kim H, Mittal D, Iadarola M, Dionne RA. Genetic predictors for acute experimental cold and heat pain sensitivity in humans. *J Med Genet* 2006;43(8):e40.
PUBMED | **CROSSREF**

22. Fillingim RB, Kaplan L, Staud R, Ness TJ, Glover TL, Campbell CM, et al. The A118G single nucleotide polymorphism of the mu-opioid receptor gene (OPRM1) is associated with pressure pain sensitivity in humans. *J Pain* 2005;6(3):159-67.
PUBMED | **CROSSREF**

23. Tegeder I, Costigan M, Griffin RS, Abele A, Belfer I, Schmidt H, et al. GTP cyclohydrolase and tetrahydrobiopterin regulate pain sensitivity and persistence. *Nat Med* 2006;12(11):1269-77.
PUBMED | **CROSSREF**

24. Kim H, Neubert JK, San Miguel A, Xu K, Krishnaraju RK, Iadarola MJ, et al. Genetic influence on variability in human acute experimental pain sensitivity associated with gender, ethnicity and psychological temperament. *Pain* 2004;109(3):488-96.
PUBMED | **CROSSREF**

25. Evans PJ. Narcotic addiction in patients with chronic pain. *Eur J Pain* 1981;36(6):597-602.
PUBMED | **CROSSREF**

26. Schug SA, Zech D, Grond S, Jung H, Meuser T, Stobbe B, et al. A long-term survey of morphine in cancer pain patients. *J Pain Symptom Manage* 1992;7(5):259-66.
PUBMED | **CROSSREF**

27. Højsted J, Sjøgren P. Addiction to opioids in chronic pain patients: a literature review. *Eur J Pain* 2007;11(5):490-518.
PUBMED | **CROSSREF**

28. Passik SD, Schreiber J, Kirsh KL, Portenoy RK. A chart review of the ordering and documentation of urine toxicology screens in a cancer center: do they influence patient management? *J Pain Symptom Manage* 2000;19(1):40-4.
PUBMED | **CROSSREF**

29. Jadad AR, Rizo CA, Enkin MW. I am a good patient, believe it or not. *BMJ* 2003;326(7402):1293-5.
PUBMED | **CROSSREF**

30. Sointu E. 'Good' patient/'bad' patient: clinical learning and the entrenching of inequality. *Sociol Health Illn* 2017;39(1):63-77.
PUBMED | **CROSSREF**

31. Freeman G, Barclay J. Comparison of the risk for substance abuse in heart failure and cancer patient populations using the Opioid Risk Tool and urine drug screen (SA508D). *J Pain Symptom Manage* 2017;53(2):397-8.
CROSSREF

32. Lakha SF, Louffat AF, Nicholson K, Deshpande A, Mailis-Gagnon A. Characteristics of chronic noncancer pain patients assessed with the opioid risk tool in a Canadian tertiary care pain clinic. *Pain Med* 2014;15(10):1743-9.
PUBMED | **CROSSREF**

33. Witkin LR, Diskina D, Fernandes S, Farrar JT, Ashburn MA. Usefulness of the opioid risk tool to predict aberrant drug-related behavior in patients receiving opioids for the treatment of chronic pain. *J Opioid Manag* 2013;9(3):177-87.
PUBMED | **CROSSREF**

34. Cheatle MD, Compton PA, Dhingra L, Wasser TE, O'Brien CP. Development of the revised Opioid Risk Tool to predict opioid use disorder in patients with chronic nonmalignant pain. *J Pain* 2019;20(7):842-51.
PUBMED | **CROSSREF**

35. Oh SY, Shin SW, Koh SJ, Bae SB, Chang H, Kim JH, et al. Multicenter, cross-sectional observational study of the impact of neuropathic pain on quality of life in cancer patients. *Support Care Cancer* 2017;25(12):3759-67.
PUBMED | **CROSSREF**

36. Wiffen PJ, Wee B, Moore RA. Oral morphine for cancer pain. *Cochrane Database Syst Rev* 2016;4(4):CD003868.
PUBMED

37. Park CK, Kang HW, Oh IJ, Kim YC, Kim YK, Na KJ, et al. Once-daily OROS hydromorphone for management of cancer pain: an open-label, multi-center, non-interventional study. *J Korean Med Sci* 2016;31(12):1914-21.
PUBMED | **CROSSREF**