NIH Public Access
Author Manuscript
Clin Toxicol (Phila). Author manuscript; available in PMC 2014 July 01.

Published in final edited form as:
Clin Toxicol (Phila). 2013 July ; 51(6): . doi:10.3109/15563650.2013.811588.

Misuse of the Naranjo Adverse Drug Reaction Probability Scale in toxicology

Donna Seger[1], **Kimberly BARKER**[2], and **Candace D. McNAUGHTON**[3]

[1]Department of Medicine and Emergency Medicine, Vanderbilt University Medical Center, Nashville TN, USA

[2]Department of Pharmacy Practice, Lipscomb University College of Pharmacy, Nashville, TN, USA

[3]Department of Emergency Medicine, Vanderbilt University Medical Center, Nashville, TN, USA

Abstract

Context—When an adverse event occurs in an overdose patient, it may be difficult to determine whether the event was caused by the ingested drug or by medical therapy. Naranjo and colleagues developed a probability scale, the Naranjo Adverse Drug Reaction Probability Scale (Naranjo Scale), to assess the probability that a drug administered in therapeutic doses caused an adverse event thereby classifying the event as an adverse drug reaction (ADR). Although Naranjo et al. specifically excluded the application of this scale to adverse events in overdose patients, case reports demonstrate that authors continue to apply the Naranjo Scale to events in these patients.

Objective—The World Health Organization defines an ADR as occurring only when drugs are administered in therapeutic doses. Yet ADRs continue to be reported in overdose patients. We sought to examine the use of the Naranjo scale in case reports of overdose patients to assess the potential consequences of that application.

Methods—A Medline search via PubMed without language limits, through September 2012, using the search terms “Naranjo” and “overdose” or “poisoning” yielded 146 publications. Additional searches were performed to find articles with keywords of the Naranjo Scale development, current applications and validity of application in specific populations such as critically ill and overdose patients.

Results—From the 146 publications, we identified 17 case reports or series of overdose patients in which the Naranjo Scale was applied to a clinical complication to support a causal relationship between an administered drug and the clinical complication and thereby classify the clinical complication as an ADR. We also identified a recent publication in which the Naranjo Scale was applied to a new treatment modality (lipid emulsion) that is currently administered to overdose patients.

Conclusion—Adverse events that occur in overdose patients are excluded from the definition of ADR. Yet in case reports or series of overdose patients, the Naranjo Scale has been applied to assess the probability an event was caused by the ingested drug or therapeutic modality. This application of the Naranjo Scale is not scientifically valid and may lead to erroneous conclusions. There is no evidence to support the application of the Naranjo scale to any events that occur in overdose patients.

Address correspondence to: Kimberly Barker, Department of Pharmacy Practice, Lipscomb University College of Pharmacy, Nashville, TN 37204, USA. kim.barker@lipscomb.edu.

Declaration of Interest
The authors report declaration of interest.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Introduction

Although case reports and case series aform the basis of much of our clinical knowledge in toxicology, they have inherent limitations and frequently lack critical information. A review of 1520 case reports of ADRs revealed that many of the reports lacked important information such as serum drug concentration, dose of the drug, duration of therapy and clinical/laboratory values such as renal function.[1] Fewer than 1% provided an objective assessment of causality. One of the tools that we are using in an attempt to gain knowledge from the case report is the Naranjo Scale. To understand the implications of misapplication of the Naranjo Scale to overdose patients, one must first understand the development and validity of the Naranjo Scale, and how subsequent applications to different patient group have evolved. The objective of this review is to describe the development and purpose of the Naranjo Scale and assess the potential consequences of applying the Naranjo scale to overdose patients.

Background

Naranjo Scale Development

Prior to 1981, the Kramer algorithm, used to assess the likelihood that an adverse clinical outcome resulted from an administered drug (and was therefore an ADR), was a cumbersome decision strategy with six axes.[2] Naranjo et al. proposed a much simpler probability scale designed to sensitively "monitor ADRs and…to [perform] post marketing drug surveillance" and to improve inter-rater reliability[3] This scale would allow categorical classification of ADRs as "definite", "probable", "possible" or "doubtful" based on the answers to 10 questions. First, Naranjo et al. defined ADR (consistent with the World Health Organization definition) as "any noxious, unintended, and undesired effect of a drug after doses used in humans for prophylaxis, diagnosis or therapy. This definition excludes therapeutic failures, intentional and accidental poisoning, and drug abuse." Then six investigators (two physicians and four pharmacists) reviewed 63 randomly selected ADRs reported in the peer-reviewed literature. They devised 10 questions, each with answers of "yes," "no," and "do not know" and used an empiric weighted scoring system for the answers. An answer of "yes" to a question received a score of −1, +1 or +2. An answer of "no" to a question received a score of −1, 0, +1 or +2. The answer "don't know" received a score of 0. The sum of the scores from the ten questions ranged from negative four (−4) to +13 and was interpreted to reflect the strength of the causal relationship (Table 1), i.e., the probability that a drug had caused an ADR and that the complication was not a manifestation of the disease. A sum greater than nine was empirically defined as "definitely" having caused the ADR; a sum of five to eight "probably" caused the ADR; a sum of one to four "possibly" caused the ADR; and a score less than one indicated association with drug was "doubtful". Reliability was evaluated by randomly rescoring the same 63 cases at three different time periods (initial evaluation, then at six weeks and 10 months). Consensus of three "experts" with the six raters was high, as was the agreement between the physician-pharmacists and one expert. Naranjo et al. evaluated the reliability and validity of the Naranjo Scale in developing consensus among reviewers. Consensus validity was evaluated by comparing the Naranjo Scale against the external standard of physician-pharmacist assessment of the relationship between a drug and ADR. Content validity was evaluated using the 63 reported cases and 28 prospectively collected cases. Variations in the ADR scores were compared to the scores of events that were definitely not an ADR. Concurrent validity was evaluated by comparing the Naranjo scores against the scores derived from Kramer's algorithm (based on six axes of decision strategy) ($r=0.082$, $p<0.001$). Naranjo et al. demonstrated that their ADR probability scale "improved reproducibility in assessments" between observers. It is worth repeating that cases of poisoning were excluded from the definition of ADR, and therefore no cases of poisoning were evaluated in this original paper.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Limitations of the Naranjo Scale

Naranjo et al. acknowledged that this scale improved reproducibility in assessments but that only experience would confirm its utility in clinical practice.[1] Even when applied in therapeutic settings, the scale has significant limitations. High inter-rater reliability may occur because two questions are consistently answered “yes”. If the medication was administered prior to development of the ADR, Question 2 receives a score of +2, placing the event in the “possible ” probability (of causing an ADR) even before any other questions are answered. A “yes” answer to a second question, for example if the event was directly observed by a health professional, yields a +1 answer score, which also places the event in the “possible” probability category.

The original 63 cases used to develop the scale are not described or referenced but are “available upon request”. However, we were unable to contact the authors of this 33-year-old paper to obtain the original cases. Therefore, the clinical details from the cases used to develop the scale are not known, including facts such as age of patient, whether patients were ambulatory, critically ill, or taking multiple drugs. The majority of the summed scores for the 63 cases ranged from 3–6 (“probably” caused the ADR). The Naranjo Scale is designed to deal with both dose-related and non-dose-related ADRs. However, as points are given for dose-response and toxic blood concentrations, idiosyncratic ADRs will not have high scores indicating a definite or probable ADR. Therefore, a midrange score may be interpreted as either the drug causing the event, or the drug not causing the event.

The 63 cases used to develop the Naranjo Scale may not have provided a large enough sample. Approximately 10 cases are required for each item on a scale to evaluate characteristics such as reliability.[4] Therefore, because there are 10 questions on the Naranjo Scale, approximately 100 cases would have been required to develop the 10-item Naranjo Scale; a smaller sample size may result in a less sensitive, less reliable scale that may not adequately identify cases of ADR.

The basis of the Naranjo Scale is consensus and expert opinion. Although consensus of experts is sometimes all that is available, we must remember the difference between consensus and science. Science is reproducible. Consensus involves opinion and politics as well.

The Naranjo Scale in critically ill patients in hospital settings

The Naranjo Scale may not be applicable to evaluate adverse events occurring in the hospital or the intensive care unit (ICU) setting, or to evaluate if a drug caused organ damage. To shed more light on this issue, we compare the Naranjo Scale to other ADR scales that have been applied to adverse events occurring in hospitalized and critically ill patients.

Lanctot and Naranjo compared the Naranjo Scale to the Bayesian Adverse Reactions Diagnostic Instrument (BARDI), a scale that calculates the post-test probability of a drug causing an ADR based on epidemiologic and case information (i.e., time of onset).[5] Over five years, they collected the following cases from an ADR clinic and pharmaceutical companies: 91 cases of hypersensitivity; 12 cases of hematologic toxicity; and three cases of pulmonary fibrosis. The methods used to obtain cases from pharmaceutical companies are not explained in detail. The Naranjo Scale weakly correlated with BARDI (correlation coefficient of 0.45; $p<0.001$) in determining whether an event was an ADR. BARDI better distinguished adverse events that were highly probable or highly improbable ADRs, whereas the Naranjo Scale scored these events in the midrange. BARDI does not have preset weightings and has flexibility to incorporate any information, while the Naranjo Scale uses average weightings of information that must be fit into existing questions. BARDI may

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

better discriminate drug from nondrug-induced cases, especially when serious adverse events occur.

Kane-Gill et al. evaluated the reliability and validity of the Naranjo Scale in a sample of ADRs that occurred in an ICU and found only marginal inter-rater agreement, with a kappa, or a measure of agreement above that expected by random chance, of 0.14 to 0.33.[6] (A kappa of 0.40–0.60 reflects moderate agreement, 0.70–0.80 reflects good agreement, and >0.81 reflects very good agreement.) Limitations to use of the Naranjo score in the intensive care include the inability to re-challenge patients (Question 4), inapplicability of placebo administration (Question 6), possible lack of serum drug concentrations (Question 7), and clarification of objective measurement (Question 10). In addition, sample size calculations for this study indicate that 122 cases of ADRs would have been required to provide adequate power.

Further questioning the appropriateness of the Naranjo Scale in an ICU setting, Du et al. applied the Naranjo Scale in three neonatal intensive care units and found moderate inter-rater reliability compared to a neonate specific ADR probability scale developed by the authors (0.42 vs. 0.62, $p < 0.001$).[7]

Application of the Naranjo Scale to determine the cause of drug-induced hepatotoxicity[8–10] reveals poor inter-rater reliability and poor correlation with external reference standards. The limitations noted with intensive care patients, including inability to re-challenge with the drug in question and lack of placebo administration, also limit the appropriate use of the Naranjo Scale for patients who develop hepatotoxicity while receiving therapeutic doses of medications. The liver-specific Council for International Organizations of Medical Sciences/ Roussel Uclaf Causality Assessment Method scale (CIOMS or RUCAM scale) [10] uses expert opinion to estimate the probability that a drug caused drug-induced liver injury (DILI). The authors applied the CIOMS and the Naranjo Scale to 225 consecutive patients in the Spanish Registry of Hepatotoxicity. The Spanish Registry consists of cases submitted at the discretion of clinicians who have determined the likelihood of DILI based on the temporal relationship between hepatotoxicity and the administration of a drug and resolution of symptoms and after excluding other causes of liver disease. The liver-specific CIOMS demonstrated much better inter-rater reliability (kappa of 0.71; 95% confidence interval 0.65–0.78) than the Naranjo Scale, (kappa of 0.17; 95% CI 0.11–0.24). Evaluating its ability to detect cases in which the CIOMS/RUCAM score was ≥6, or “definite/probable,” the Naranjo Scale demonstrated a 54% sensitivity, 88% specificity, 95% positive predictive value and a 29% negative predictive value for DILI.[10] In other words, the Naranjo Scale detected 54% of the ADRs identified by the CIOMS/RUCAM, and 12% of the time the Naranjo Scale suggested an ADR was caused by a drug when the CIOMS/RUCAM did not. In summary, the Naranjo Scale seems to have little applicability in critically ill patients.

The Naranjo Scale in overdose patients

The Naranjo Scale specifically excludes poisoning in the definition of an ADR.[1] Despite this, the Naranjo Scale has been applied with increasing frequency to overdose patients, ostensibly to determine whether an adverse event was caused by a therapeutic intervention. This application erroneously presumes that an adverse event in a poisoned patient could be an ADR. There is no definition of ADR that we could find that includes poisoning.

Methods

A Medline search via PubMed without language limits, date through September 2012, using the search terms “Naranjo” and “overdose” or “poisoning” yielded 146 publications. Additional searches were performed to find articles with keywords of the Naranjo Scale

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

development, current applications and validity of applications in specific populations such as critically ill and overdose patients.

Results

A review of the abstracts of the 146 publications revealed only 17 were case reports of patients with overdoses (Table 2).[11–27] Publications of "poisoning" resulting from therapeutic doses were excluded. Ten of these 17 cases were published in *Annals of Pharmacotherapy*, a peer-reviewed journal focused on advancements in pharmacotherapy that requires the authors to provide a Naranjo Scale score or other validated probability scale in order to publish a case report of an ADR.[28] Although other journals may not require use of the Naranjo Scale, reviewers may have encouraged authors to apply it to their case report. Fourteen of the 17 case reports do not provide a description of the Naranjo Scale but provide the rating (i.e. "probable" or "Naranjo score 5"). None of the case reports describe the individual scores for each question on the Naranjo Scale. None of these authors provide support for the use of Naranjo Scale in overdose patients, nor are there any editorials challenging the use of this scale in this setting. Unfortunately, the Naranjo Scale seems to have become—in error—an accepted tool for determining whether adverse events in overdose patients are ADRs caused by a therapeutic treatment modality.

DISCUSSION

While only 17 overdose cases were found out of the larger body of case reports of overdose in the medical literature, the acceptance of this as an appropriate tool in cases of poisoning should be addressed before it becomes more widely used. Inappropriate use of the Naranjo Scale could potentially lead to erroneous conclusions regarding the treatment of poisoned patients. Recently, Geib et al. applied the Naranjo Scale to nine poisoned patients in cardiovascular collapse who received intravenous lipid emulsion (ILE) to determine if adverse events were caused by administration of ILE.[29] Scores of the individual questions in the Naranjo Scale were not reported, nor were the scores reported for the other drugs the patients received. Death in four of the nine patients received a Naranjo Scale score of −2 or −3, indicating that it was doubtful" that death was caused by ILE. Acute Lung Injury (ALI) occurred in three survivors and received Naranjo scores of 1, which indicates ALI was "possibly" caused by ILE. Other events which were "possibly" ADRs caused by ILE included diabetic ketoacidosis, anoxic brain injury, acute renal failure, decubitus ulcer, sepsis, short term memory loss, aspiration, metabolic acidosis, sever hyperthermia, and others. Lipemia occurred in three patients and received Naranjo scores of 7 indicating that it was "probably" an ADR caused by ILE.

One can see some of the problems in applying the Naranjo Scale to evaluate adverse events occurring in these patients. Lipemia is an expected and intended effect of ILE administration, not an ADR. It was definitely caused by ILE. Some ADRs listed under "possible," (anoxic brain injury, toe amputation, ventilator-dependent respiratory failure, deep vein embolus) occur frequently in the setting of circulatory collapse and hypotension. There must be a strong consideration that these complications were caused by the ingested agent and not by ILE and therefore represent adverse events but not ADRs. Based on biological mechanism, it is difficult to understand how other adverse events (diabetic ketoacidosis, delirium, hypoglycemia) could be related to ILE administration.

Because the patients treated with ILE were critically ill, a Naranjo score of at least +2 (an adverse event appearing after suspected drug was administered scored +2) could apply to any resuscitative agents given within the same time period as ILE. The Naranjo Scale score for any therapeutic agent would indicate that the therapeutic agent "possibly" or "probably "

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

caused the adverse event merely based on the order of events, the fact that the events were witnessed by a health care provider, and because the adverse event was confirmed by objective evidence. One can see the confusion; nine patients in cardiovascular collapse are at risk for many complications even if no therapeutic agents are administered. Were poor clinical outcomes related to the underlying critical illness adverse events, or were they related to the administration of ILE? With the available clinical data, one cannot determine the cause of the adverse event in this group of patients. In order to prove that a therapeutic agent caused an event, it is necessary to establish that the adverse event occurred more often in patients who were administered the agent when compared against similar patients who did not receive the agent. For instance, in the nine patients in cardiovascular collapse, the risk of adverse events must be proven to be *higher* than the baseline risk of adverse events, i.e., higher than the risk of adverse events in other similarly poisoned patents not treated with ILE.[29] These criteria were not met in this study. But lack of statistical evidence is not a basis to apply a probability scale that is not applicable to overdose patients; the conclusions can be very misleading. Once again, a caveat in the original Naranjo paper defining its appropriate use, excluded overdose patients and stated if more than one drug was administered, the scale should be applied to all agents

Conclusion

The Naranjo Scale was originally developed to achieve consensus between reviewers in estimating the probability that an adverse event following the administration of a therapeutic dose was an ADR. It has not been validated for use in patients that are critically ill, suffer specific organ toxicity or overdose.

Yet in case reports/series of overdose patients, the Naranjo Scale has been applied to therapeutic effects (e.g., lipemia) of a treatment modality or to adverse clinical events to determine whether the event was caused by the ingested drug or by the treatment modality. Application of the Naranjo Scale in the overdose setting is not scientifically valid. Erroneous conclusions may be formed regarding treatment modalities when the Naranjo Scale is applied to events occurring in overdose patients.

References

1. Kelly WN. The Quality of Published Adverse Drug Event Reports. Ann Pharmacother. 2003; 37:1774–8. [PubMed: 14632590]
2. Kramer MS, Leventhal JM, Hutchinson TA, Feinstein AR. An algorithm for the operational assessment of adverse drug reactions. I. Background, description, and instructions for use. JAMA. 1979; 242:623–32. [PubMed: 449002]
3. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981; 30:239–45. [PubMed: 7249508]
4. DeVellis, RF. Scale Development: Theory and Applications. 2003.
5. Lanctot KL, Naranjo CA. Comparison of the Bayesian approach and a simple algorithm for assessment of adverse drug events. Clin Pharmcol Ther. 1995; 58:692–8.
6. Kane-Gill SL, Kirisci L, Pathak DS. Are the Naranjo criteria reliable and valid for determination of adverse drug reactions in the intensive care unit? Ann Pharmacother. 2005; 39:1823–7. [PubMed: 16204392]
7. Du W, Tutag Lehr V, Lieh-Lai M, et al. An Algorithm to Detect Adverse Drug Reactions in the Neonatal Intensive Care Unit: A New Approach. J Clin Pharmacol. 2012 Jan 18. Epub ahead of print.
8. Teschke R, Schmidt-Taenzer W, Wolff A. Spontaneous reports of assumed herbal hepatotoxicity by black cohosh: is the liver-unspecific Naranjo scale precise enough to ascertain causality? Pharmacoepidemiol Drug Saf. 2011; 20:567–82. [PubMed: 21702069]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

9. Liss G, Lewis JH. Drug-induced liver injury: what was new in 2008? Expert Opin Drug Metab Toxicol. 2009; 5:843–60. [PubMed: 19505188]
10. Garcia-Cortes M, Lucena MI, Pachkoria K, Borraz Y, Hidalgo R, Andrade RJ. Evaluation of naranjo adverse drug reactions probability scale in causality assessment of drug-induced liver injury. Aliment Pharmacol Ther. 2008; 27:780–9. [PubMed: 18284654]
11. Velez LI, Shepherd G, Roth BA, Benitez FL. Serotonin syndrome with elevated paroxetine concentrations. Ann Pharmacother. 2004; 38:269–72. [PubMed: 14742765]
12. DeFrates LJ, Hoehns JD, Sakornbut EL, Glascock DG, Tew AR. Antimuscarinic intoxication resulting from the ingestion of moonflower seeds. Ann Pharmacother. 2005; 39:173–6. [PubMed: 15572604]
13. Gregory MD, Mersfelder TL, Jamieson T. Accidental overdose of tiotropium in a patient with atrial fibrillation. Ann Pharmacother. 2010; 44:391–3. [PubMed: 20118141]
14. Close BR, Banks CJ. Seizures secondary to lamotrigine toxicity in a two-year-old. Ann Pharmacother. 2010; 44:1112–5. [PubMed: 20407029]
15. Kearney T, Tu N, Haller C. Adverse drug events associated with yohimbine-containing products: a retrospective review of the California Poison Control System reported cases. Ann Pharmacother. 2010; 44:1022–9. [PubMed: 20442348]
16. Kruithof MK, Bruins NA, van Roon EN. Coma after overdose with duloxetine. Ann Pharmacother. 2011; 45:e5. [PubMed: 21177420]
17. Sokoro AA, Zivot J, Ariano RE. Neuroleptic malignant syndrome versus serotonin syndrome: the search for a diagnostic tool. Ann Pharmacother. 2011; 45:e50. [PubMed: 21878660]
18. Christenson BJ, Marjala AR. Two cases of sudden sensorineural hearing loss after methadone overdose. Ann Pharmacother. 2010; 44:207–10. [PubMed: 20028962]
19. Schier JG, Howland MA, Hoffman RS, Nelson LS. Fatality from administration of labetalol and crushed extended-release nifedipine. Ann Pharmacother. 2003; 37:1420–3. [PubMed: 14519033]
20. Bromley J, Hughes BG, Leong DC, Buckley NA. Life-threatening interaction between complementary medicines: cyanide toxicity following ingestion of amygdalin and vitamin C. Ann Pharmacother. 2005; 39:1566–9. [PubMed: 16014371]
21. Phan H, Casavant MJ, Crockett S, Lee A, Hall MW, Nahata MC. Serotonin syndrome following a single 50 mg dose of sertraline in a child. Clin Toxicol (Phila). 2008; 46:845–9. [PubMed: 18608268]
22. Brucculeri M, Kaplan J, Lande L. Reversal of citalopram-induced junctional bradycardia with intravenous sodium bicarbonate. Pharmacotherapy. 2005; 25:119–22. [PubMed: 15767228]
23. Steidl KE, Darko W, Probst LA, Noviasky JA, Nasser S. Rhabdomyolysis associated with phentermine. Am J Health Syst Pharm. 2010; 67:1929–32. [PubMed: 21048209]
24. Fathallah N, Zamy M, Slim R, et al. Acute pancreatitis in the course of meprobamate poisoning. Jop. 2011; 12:404–6. [PubMed: 21737904]
25. Fernandes R. Acute pancreatitis following paracetamol overdose. BMJ Case Rep. 2009; 2009
26. Nelson H, Katz D, Dunn T, et al. Rhabdomyolysis and necrotic bowel after acetaminophen and ibuprofen overdose. Pharmacotherapy. 2007; 27:608–12. [PubMed: 17381389]
27. Mullins ME, Vitkovitsky IV. Hemolysis and hemolytic uremic syndrome following five-fold N-acetylcysteine overdose. Clin Toxicol (Phila). 2011; 49:755–9. [PubMed: 21970774]
28. [Accessed May 9, 2013] Annals of Pharmacotherapy: author instructions. http://www.theannals.com/site/misc/author-info.xhtml
29. Geib AJ, Liebelt E, Manini AF. Clinical experience with intravenous lipid emulsion for drug-induced cardiovascular collapse. J Med Toxicol. 2012; 8:10–4. [PubMed: 21989640]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Table 1

ADR probability scale

The Naranjo Scale questions and weighted scores [1]

To assess the adverse drug reaction, please answer the following questionnaire and give the pertinent score.				
	Yes	**No**	**Do not know**	**Score**
1. Are there previous *conclusive* reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	−1	0	
3. Did the adverse reaction improve when the drug was discontinued or a *specific* antagonist was administered?	+1	0	0	
4. Did the adverse reaction reappear when the drug was readministered?	+2	−1	0	
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	−1	+2	0	
6. Did the reaction reappear when a placebo was given?	−1	+1	0	
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in *any* previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	
			Total Score	

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

Table 2

Summary of published manuscripts of overdoses reporting use of the Naranjo Scale

Reference	Suspected agent – ADR	Naranjo score/comments by the authors
Velez, et al.[11]	Paroxetine – Serotonin Syndrome	"Use of the Naranjo probability scale indicated a probable relationship between the serotonin syndrome and the overdose taken by this patient"
DeFrates, et al.[12]	Moonflower seeds – antimuscarinic intoxication	"Use of the Naranjo probability scale suggests a possible relationship between the moonflower seed ingestion and the resulting anticholinergic intoxication"
Gregory, et al.[13]	Tiotropium – atrial fibrillation	"Use of the Naranjo probability scale confirmed a causative relationship as a probable drug effect"
Close, et al.[14]	Lamotrigine – seizures	"The Naranjo probability scale suggested a probable causality between the acute lamotrigine ingestion and seizures"
Kearney, et al.[15]	Yohimbine – multiple	"Eligible patients involved adults aged 18 years and older with a reported ingestion of a yohimbine- containing product who were symptomatic with a Naranjo causality score of 1 (possible) or better (as determined by the investigators)"
Kruithof, et al.[16]	Duloxetine – coma	"Use of the Naranjo adverse drug reaction probability scale indicated that the adverse effects were probably caused by duloxetine overdose"
Sokoro, et al.[17]	Neuroleptic malignant syndrome (NMS) vs. serotonin syndrome – diagnostic tool	"The Naranjo probability scale indicated a probably causality association between NMS and quetiapine, haloperidol, and resperidone in our patient, whereas it assigned only a possible causality association for serotonergic agents and development of serotonin syndrome"
Christenson, et al.[18]	Sensorineural hearing loss (SSHL) – methadone	"We believe methadone to be the probably cause of SSHL in both patients as show with use of the Naranjo probability scale, since the adverse event appeared after toxic concentrations of methadone were administered and the symptoms improved when the drug was eliminated from the body."
Schier, et al.[19]	Death – labetalol and nifedipine	"Use of the Naranjo probability scale indicated a highly probable relationship between this patient's hypotension and her nifedipine and labetalol therapy"
Bromely, et al.[20]	Cyanide toxicity – amygdalin and vitamin C	"On the Naranjo probability scale, the adverse drug reaction was rated probable"
Phan, et al.[21]	Serotonin syndrome – sertraline	"The Adverse Drug Reaction Probability Scale by Naranjo et al. is a validated causality scale…the final tabulated score was a 6, indicating an association between the single dose of sertraline and serotonin syndrome in our patient as 'probable'."
Brucculeri, et al.[22]	Reversing bradyarrhythmia – sodium bicarbonate	"In the case that we have just described, the Naranjo probability scale for adverse drug reactions indicates that sodium bicarbonate was probably responsible for the reversal of bradyarrhythmia in our patient"
Steidl, et al.[23]	Rhabdomyolysis – phentermine	"The Naranjo et al. adverse event probability scale indicated a probable relationship between phentermine and rhabdomyolysis (probability score of 5)"
Fathallah, et al.[24]	Acute pancreatitis – meprobamate	"According to the Naranjo probability scale, meprobamate-induced acute pancreatitis was probable."
Fernandes[25]	Acute pancreatitis – paracetamol	"The assessment of the probability of an adverse drug reaction is problematic. The Naranjo adverse drug reaction probability scale is commonly used in clinical practice. Implementation of this probability scale yielded a score of 5, which correlates to a probable adverse drug reaction association. There were some elements of the scoring system that could no be assessed due to ethical reasons (eg. did the adverse reaction reappear when the drug was readministered?)"
Nelson, et al.[29]	Rhabdomyolysis and necrotic bowel – ibuprofen	"Using the Naranjo adverse drug reaction probability scale, a score of 5 was derived, which indicates that the likelihood of the necrotic bowel being drug related was probable."
Mullins, et al.[27]	Hemolysis and hemolytic uremic syndrome – N-acetylcysteine	"Using the Naranjo scoring system for adverse drug reactions (ADRs), this event receives 5 points out of a maximum of 13, which places it in the "probable" category. However, the Naranjo score was designed and studied primarily as a means of improving inter-rater agreement in classifying cases rather than to be highly sensitive and precise in evaluating possible ADRs,

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Reference	Suspected agent – ADR	Naranjo score/comments by the authors
		and several of the questions are not applicable to all cases. Some authors have questioned its utility.