pISSN 2454-5929 | eISSN 2454-5937

Original Research Article

DOI: http://dx.doi.org/10.18203/issn.2454-5929.ijohns20200131

Side effects of medications in professional opera singers' voice: survey findings

Pedro Clarós^{1*}, Kinga Mikolajczyk², Astrid Clarós Pujol¹, Carmen Pujol¹, Juan Sabater³, Andrés Clarós¹

Received: 04 July 2019 Revised: 10 October 2019 Accepted: 19 December 2019

*Correspondence: Dr. Pedro Clarós,

E-mail: clinica@clinicaclaros.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Background: Opera singers are classified under level I, as the elite vocal performers, being the quintessential representatives of this group. As the professional voice users, they meticulously observe any changes relevant to their health, therefore self-reported side effects should be taken under serious consideration. The aim of this study was to initiate the process of gathering general information about the most common side effects of medications taken by the opera singers.

Methods: The study group consisted of 264 professional opera singers, treated in Clarós Clinic in a 35 years period, who were asked to complete a questionnaire. The response rate was 62.1% (n=164) with a male-to-female ratio being 1.27:1 (72 men and 92 women). 46 cases of adverse effects of medicines were updated and analysed. All the responses were collected between February and April 2018.

Results: The mean age of our study group was 38.3 for females and 49.95 for males, with the range between 18-83 years. The vocal categories were as follows: 39 tenors, 17 baritones, 14 basses, 64 sopranos, 23 mezzo-sopranos and 5 contraltos. Patients with chronic diseases and comorbidities represented the 39.1% of the study group. The most common adverse effect reported was dryness (15.2%). The most frequent voice side effects raised by singers were clearing the throat frequently (14.63%), hoarseness and coarse or scratchy sound (10.37%), and vocal fatigue (7.32%). **Conclusions:** We believe that exploring the subject of vocal side effects of medications in professional opera singers is extremely important.

Keywords: Side effects, Drugs, Opera singers, Nucleotide polymorphisms

INTRODUCTION

Opera singers, according to Koufman, are classified under level I, as the elite vocal performers, being the quintessential representatives of this group. Even a negligible alteration to laryngeal function might cause significant consequences for them.

Named as vocal athletes, they have to work in highly competitive and demanding circumstances, both because of vocal performance and stressful lifestyle. Hence, as the professional voice users, they meticulously observe any changes relevant to their health, with particular emphasis on any vocal abnormalities. The performers' voice is susceptible to diverse psychological and environmental factors (like smoke or poor humidity), and most of all, a

¹Department of ENT, Clinica Clarós, Barcelona, Spain

²Department of ENT, Ludwik Rydygier Memorial Specialized Hospital, Cracow, Poland

³Department of Biochemistry, Faculty of Pharmacy, Barcelona University, Barcelona, Spain

lot of medications may influence the proper function of singer's inner instrument, which is irreplaceable.^{3,4}

One of the most popular drugs affecting voice are antihistamines, whereas allergy is the second most common chronic disease in adult population. Most of antihistamines have the drying effect, what causes a decreased level of vocal fold lubrication, frequent coughing, and increased throat clearing. Salatoff emphasises how troublesome these medications are, especially as many of them are available without prescription. Moreover, they are often combined with parasympatholytics, which causes the thickening of mucosa and reduction of mucosal secretion.

Another popular group of medications are steroids. Inhaled corticosteroids may induce vocal side effects like hoarseness, dysphonia, mild mucosal drying, cough, and oral or laryngopharyngeal candidiasis or thrush. Similar problems apply to oral steroids. This group of drugs cause one of the most various effects, like gastrointestinal upset and ulcers, increased appetite, mucosal drying, blurred vision, and aggravation of blood glucose levels, or even delirium, depression, insomnia, mania, and psychoses. For a professional singer these potential effects can be especially bothersome. It is also important to administer steroids especially carefully, because of the risk of mucosal damage and inflammation, and in consequence, vocal fold haemorrhage or laryngitis.

Subsequent group of drugs, which have the potential to dry/damage the mucosa and, in consequence, disrupt phonation process, are diuretics. Although they do not effectively mobilise water from vocal fold tissues, they increase viscosity of secretions causing a lot of difficulties in singing process.

Medications for gastroesophageal reflux disease like proton pump inhibitors (PPI's) may lead to diarrhoea, nausea, vomiting, regurgitation, upper respiratory tract infections, cough, or dry mouth.⁸

Finally, aspirin as one of the most widely known drug has the tendency to cause bleeding (vocal fold haemorrhage), which can be devastating for voice and, in consequence, may terminate the professional career.

To the best knowledge of the authors opera singers were never tested and never asked about their symptoms. What makes the group of professional voice users unique is the fact that they are relatively healthy and take as little medications as possible because of the fear of losing the full ability of phonation and possibility to perform on the stage without any distributions. They are aware that drugs' side effects may in consequence damage the voice or even totally end the career. As very sensitive and focused group they can easily distinguish if the symptoms are caused by the particular medication or other factor.

The aim of the study was to initiate the process of gathering general information about the most common side effects of medications taken by the opera singers to improve the quality of medical management and knowledge of the healthcare providers. The research was designed as a retrospective observational study.

METHODS

Study design

A two-page survey consisting of 16 questions was designed by the authors to measure variables concerning different aspects of demographical data including the gender, age, tessitura, weight, height, body mass index, performing status, allergies, fluids, alcohol intake, and smoking. Moreover, the questionnaire included information about chronic diseases, administered medications, and possible side effects.

Adverse effects concerning voice quality changes were divided into 14 options (Appendix). Additionally, there was a free space available for personal comments about side effects affecting voice, in case of answers not included in the list. The intensity of side effects was expressed on the ten-point scale of severity. The onset of adverse effects was classified into the one of two categories: accruing at the beginning or later. The questionnaire was provided in English and Spanish language. The data was gathered retrospectively. Qualitative and quantitative data was collected contemporaneously from completed surveys.

The study place and period

The survey was responded directly during medical consultations or, if the presence in the office was impossible, over telephone calls or sent by an e-mail to approximately 264 professional opera singers in Spain and all around the world. 38% of questionnaires were sent by an e-mail to the performers who were abroad or preferred this way of contact. All the responses were collected between February and April 2018.

Selection criteria, procedure and ethical approval

The present study was approved by Clarós Clinic Medical Committee. Patients' informed consents were obtained mostly during medical consultations. Respondents who completed the questionnaire via phone calls or e-mail, sent the researchers a signed paper by mail or photographs with their consent. Their personal data (considered as sensitive) were double coded. Professional opera singers were asked to use initials in questionnaires, afterward, the initials were converted into numerical codes, to stay confidential (e.g., to avoid recognizing famous patients by the statistician). Participants were informed that the study was created to explore the medications intake and occurrence of possible adverse effects.

Statistical analyses

Student's t-test was used to compare three groups according to differences in the parameters of interest. Gathered data was checked for normal distribution prior calculations. Frequencies/standard deviations and means (±SD) were used to describe the collected data for categorical and continuous variables, respectively. Standard deviations and means were calculated for variables with normal distribution. quantitative Categorical variables were expressed as proportions. Spearman correlation coefficient was used to analyse a correlation between the occurrence of chronic diseases and side effects on voice. All analyses were conducted using the program Statistica version 13.1 (Elliott Management Corporation, New York, USA). The level of statistical significance was considered at p<0.05 for all tests.

RESULTS

Participants

The patients included in the study were professional opera singers who have received medical care at the Clarós Otorhinolaryngology Clinic in Barcelona during the last 35 years, both performers and masterclass teachers. Two hundred sixty-four professional opera singers were studied using questionnaire. The response rate was 62.1%. Of the 164 patients studied, 92 (56%) were females and 72 (44%) were males. The mean age was 43±16.2, with the range between 18-83 years old (Figure 1).

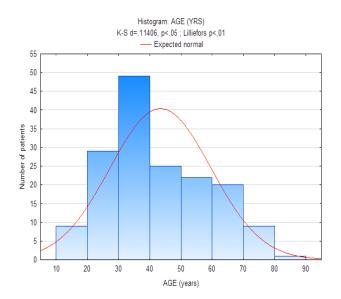


Figure 1: Participants' age histogram.

Demographics

The analysed data were divided into three groups based on the age of professional opera singers, as following: group A, singers over 18 to 29 years old; group B, singers 30-45 years old; and group C, singers 46-83 years old. The majority of females were in group B (60% of the group), whereas the males dominated in the oldest age group was 62% (Table 1). Among the women 69 singers were in the reproductive age and 21 in postmenopausal (all included only in population C).

Table 1: Results of descriptive statistics in relation to demographical data.

		Population A 18-29 years (n=32)	Population B 30-45 years (n=70)	Population C 46-83 years (n=62)
Number of patients N (%)		32 (20)	70 (43)	62 (38)
Median age (years)		23.18±3.5	36.85±4.3	61.27±9.1
Condon N (0/)	Female	26 (81)	42 (60)	24 (38)
Gender N (%)	Male	6 (19)	28 (40)	38 (62)
Total ratio		4.3:1	1.5:1	1:1.9
	Soprano	19	30	15
Female	Mezzo-Soprano	5	10	8
	Contralto	2	2	1
	Tenor	3	21	15
Male	Baritone	3	4	10
Maie	Bass	0	3	11
	Countertenor	0	0	2
Professional	Master class	0	0	9
activity	Performing	32	70	33
activity	Both	0	0	20

Survey results

The analyses revealed that average body mass index (BMI) was 23.14±4.5 kg/m². All but five respondents

were non-smokers (Figure 2), and almost 86% denied alcohol consumption Moreover, the data revealed a lower alcohol intake among younger than older participants (Figure 3). The mean self-reported drinking fluids was

5.76 cups/day, and water as the only drink was chosen by 104 (63.4%) opera singers (Figure 4). The vocal categories were as follows: 39 tenors, 17 baritones, 14 basses, 64 sopranos, 23 mezzo-sopranos, and 5 contraltos (Figure 5). The majority of the participants were active performing opera singers 82.3%.

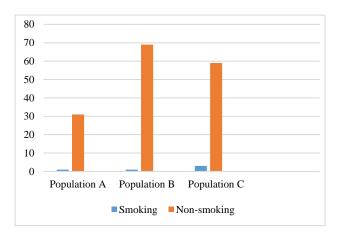


Figure 2: Participants' smoking habits.

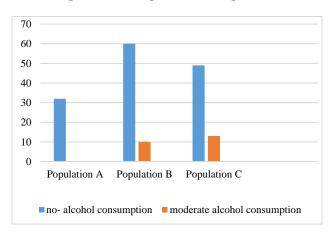


Figure 3: Participants' alcohol consumption.

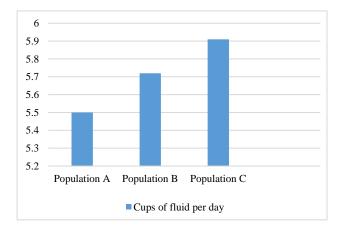


Figure 4: Participants' fluid consumption.

Few of the opera singers (9.1%) reported allergies in the survey, commonly to drugs like aspirin and penicillin, food, animals and dust.

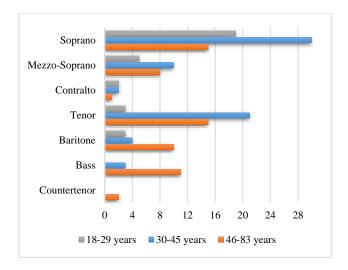


Figure 5: Participants' voice categories.

Patients with chronic diseases and comorbidities represented 39.1% (n=64) of the study group. The most commonly revealed health problems were as follows (Table 2) as hypertension (23), hypercholesterolemia (11), diabetes (7), anxiety and depression (7), hypertrophy of the prostate (4), gastroesophageal reflux disease (4), asthma (3), psoriasis (2), vascular diseases (3), and rheumatoid arthritis (3). Hypertension was the most popular disease among both genders. The vast majority had reported only one chronic disease (n=54), and two or more were found only among the professional singers from the population C. There was a positive correlation between the occurrence of chronic diseases and side effects on voice (Spearman correlation coefficient r=0.69, p<0.05).

51% of the patients declared taking the medications in the questionnaires. Table 3 and Table 5 are summarizing the results of provided answers in each of the populations. The most frequently medications used daily were: oral contraceptive pills (12%), statins (6%), oral and inhaled steroids (5%), diuretics (5%), and antihistamines (5%). Subsequently drugs administered occasionally were vitamins (16%), herbs (15%), PPI's (7%), paracetamol (5%), and nonsteroidal anti-inflammatory drugs (NSAIDs) (5%). Furthermore, the analyses revealed that more than one drug was being administered by 19 of the individuals.

Dryness (15.2%) was revealed as one of the most self-reported symptoms among opera singers who were taking medications regularly. The other widely complained vocal side effects were clearing the throat frequently (14.63%), hoarseness and coarse or scratchy sound (10.37%), and vocal fatigue (7.32%). In addition, there were no statistically significant difference in the prevalence of adverse effects of medications between males and females in particular groups. However, the side effects were reported the most frequently in elite vocal performers aged between 46 and 83 years (Table 4).

Last question of the survey had investigated the attitude of opera singers towards knowledge about the composition of the over-the-counter medicines (OTC). The results demonstrated that 71.95% of respondents

regularly check the ingredients of drugs, with the highest percentage -77% in the population C comparing to A or B -68% (Figure 6).

Table 2: Occurrence of chronic diseases and co-morbidities among participants.

	Population A 18-29 years (n=32)	Population B 30-45 years (n=70)	Population C 46-83 years (n=62)	Total
Number (%)	2 (6)	14 (20)	48 (77)	64 (39.1)
Chronic diseases and co-morbidities	Psoriasis -1 Back pain-1	Hypertension-2 Hypercholesterolemia-3 Diabetes -1 Anxiety -1 Reflux -1 Overweight-2 Depression-1 Psoriasis-1 Crohn Disease -1 Intolerance of lactose-1	Hypertension-21 Hypercholesterolemia-8 Diabetes-6 Anxiety -4 Reflux -3 Hypertrophy of prostate-4 Asthma-3 Rheumatism-3 Venous thrombosis-3 Depression-1 Cancer -1 Osteoporosis-1 Hypothyroidism-1 Arrhythmia-1	Hypertension -23 Hypercholesterolemia-11 Diabetes -7 Anxiety -5 Reflux -4 Hypertrophy of prostate-4 Asthma-3 Rheumatism-3 Venous thrombosis-3 Overweight-2 Depression-2 Psoriasis-2 Back pain -1 Cancer -1 Osteoporosis-1 Hypothyroidism-1 Arrhythmia-1 Crohn disease -1 Intolerance of lactose -1

Table 3: Summary of the types of medications taken daily by the professional opera singers.

Medications		Population A 18-29 years (n=32)	Population B 30-45 years (n=70)	Population C 46-83 years (n=62)
	Vitamins	1	0	1
	Steroids	1	1	7
	PPI's	0	1	7
	Antihistamines	1	1	1
	Antidepressants	0	2	4
	Paracetamol	0	0	1
Administered	Aspirin	0	0	2
daily	NSAIDs	1	0	0
	Hormones	0	0	3
	OC pills	11	9	0
	Statins	0	3	7
	B-blockers	0	0	4
	Diuretics	0	1	8
	ACEI	0	1	4
Total number		15 (47%)	19 (27%)	49 (79%)

Table 4: Summary of the frequency of vocal side effects among selected respondents (student's t-test).

		Population A 18-29 years (n=32)	Population B 30-45 years (n=70)	Population C 46-83 years (n=62)	Total
Side effects on voice		2	12	32	46
No side effects		30	58	30	118
Onset	From beginning	2	12	30	44
	Later	0	0	2	2

Continued.

		Population A 18-29 years (n=32)	Population B 30-45 years (n=70)	Population C 46-83 years (n=62)	Total
	Hoarseness	0	1	16	17 (p=0.0013)
	Fatigue (voice tiredness or quality changes after speaking for a short period of time)	0	2	10	12 (p=0.016)
	Volume disturbances (trouble while speaking)	0	0	3	3 (p=0.2)
	Loss of range	0	1	3	4 (p=0.14)
	Vocal tremor	0	1	2	3 (p=0.2)
	Changes in fiatto	0	1	2	3 (p=0.2)
Vocal side effect	Changes in classification (e.g., voice lowering from soprano to mezzo)	0	0	1	1 (p=0.97)
	Prolonged warm-up time (over 1/2 hour to warm-up)	1	1	2	4 (p=0.57)
	Breathiness	0	1	0	1 (p=0.97)
	Clearing throat frequently	1	8	15	24 (p=0.009)
	Tickling sensation while speaking/ foreign body sensation	0	0	3	3 (p=0.2)
	Pain in throat while speaking.	0	1	2	3 (p=0.2)
	Bitter or acid taste- bad breath	1	3	2	6 (p=0.78)
	Dryness	1	7	17	24 (p=0.004)

Table 5: Summary of the medications taken occasionally by the professional opera singers.

Medications		Population A 18-29 years (n=32)	Population B 30-45 years (n=70)	Population C 46-83 years (n=62)
	Vitamins	5	12	8
	Herbs	4	5	14
	Steroids	0	0	1
	PPI's	0	7	5
41	Antihistamines	0	5	1
Administered	Antidepressants	0	1	0
occasionally	Paracetamol	3	2	7
	Aspirin	0	1	1
	NSAIDs	3	5	4
	Diuretics	1	0	1
	Sleeping pills	0	5	3
Total number (%)		16 (50)	43 (61)	45 (73)

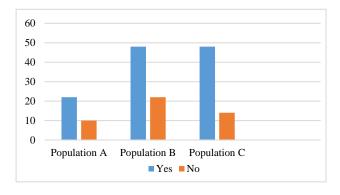


Figure 6: Participants' response to the question "do you check routinely the composition of the medications, herbals or vitamins which you can buy without prescription?".

DISCUSSION

Findings

The results of our study are preliminary, but nonetheless encouraging. Sataloff et al claims that hypochondriasis is uncommon among professional opera singers, which emphasises the fact that reported side effects should be taken under serious consideration. ¹⁰ Elite voice users are one of the most vulnerable group of patients, as they have to constantly meet high expectations. Demographical data mentioned above (domination of individuals in young age, i.e., 102 singers younger than 45 years old), good BMI (23.14 kg/m²), and extremely low alcohol and cigarettes consumption reported in our study, confirm the fact that we are dealing with especially healthy and disciplined group.

Surprisingly, the rate of responses to questionnaires sent by e-mail was extremely low, 1.9% (2 of 102). Although the surveys were anonymous, opera singers were not open to share their personal data by e-mail, whereas during direct conversation 100% agreed to answer the questions. Collecting the information directly from professional singers allowed avoiding unanswered questions as the missing values in statistic. However, the tendency to hide comorbidities and create an image of a healthy individual should be highlighted as a possible difficulty of the next studies. The other limitation of the survey was the low number of questions, which, on one hand, made it easy to answer, but, on the other hand, limited the data. The lack of specific voice measurements should be also mentioned as the limitation of the study.

Side effects regarding voice were a well-known problem in the literature, especially those for: steroids, betablockers, diuretics, statins, PPI's or antidepressants. 9-11,17 Whereas, it is important to also mention also the difficulties in distinguishing adverse effects of single drug in case of polytherapy, which was reported by as many as 23% of the patients. In that case pharmacogenomics studies should be concerned to improve the understanding of interactions between the medications. 12

Another interesting finding is that among the antihistamines being taken by the opera singers, using the representants of third generation antihistamine, levocetirizine, was not reported. The only reported antiallergic drug was ebastine (second generation, selective H1-receptor), probably because of giving less side effects such as headache, dry mouth, or drowsiness; comparing to sleepiness, tiredness, weakness, sore throat, dry mouth, fever, cough, and nosebleed, which may be caused by levocetirizine. Furthermore, no female professional singer taking oral contraceptive pills reported any side effect correlated with the voice, which supports the findings by Van Lierde et al. 14

Subsequently, none of the opera singers reported any side effect caused by herbs or other over-the-counter medications (OTCs). However, it has to be kept in mind that many of them may affect the voice and interact between other drugs.¹⁵ Surow et al states that lack of Food and Drug Administration regulations might wrongly imply safety of taking these medications. Considering the specific risk for professional voice users, it is worth avoiding medicaments with anticoagulant activity, such as aspirin, and others containing like dong quai, fennel, feverfew, willow, primrose, cowslip, ginger, garlic, Jackin-the-pulpit, ginkgo biloba, and high doses of vitamin E. Moreover, many herbs, such as elder, feverfew, dandelion or nettles, may cause diuretic effect. Finally, the most popular vitamin C can in high doses induce bloating, flatulence, diarrhoea and cramps.¹⁶

In this important clinical question about drugs' side effects, opera singers' voice as a multidimensional

parameter requires further investigation with a larger group and more sophisticated measurements. Nevertheless, our study aimed to start this process.

Importance of drug-drug-herbs interactions

Martin presents five pharmacological principles, which should be kept in mind throughout the discussion about the effects of drugs, i.e. biological response variability, placebo effect, dose-response relationship, multiple effects of a single drug, and drug efficacy versus drug dosage.¹⁷ It is assumed that in all cases the prescribed medications have been at the correct doses according to protocols. However, polypharmacy is very frequent, especially with drugs prescribed by different specialists and with self-medication (in this case mainly herbs and nutritional supplements). Therefore, in polymedication, when one drug inhibit the elimination of the other or accelerate it, the usual therapeutic doses can be toxic or insufficient due to interactions.

In our study 12% of the singers were taking contraceptive pills. Some of them, to calm their nerves, had the habit of taking an infusion of St. John's Wort. This herb, being a powerful inducer of the hepatic enzymes that eliminate the oestrogens and progestogens, may be the cause of therapeutic failure by levels below the therapeutic window, and in this case the therapeutic failure can lead to pregnancy.

From our data it is observed that 6% of the singers were taking statins. The most frequently prescribed are simvastatin and atorvastatin. If they were habitually drinking grapefruit juice, or due to an allergic process (5% of our patients) they were taking ranitidine for several weeks, a myopathy could appear due to abnormal high levels of the statins in blood and tissues. The statins could inhibit the production of CoQ10 in the muscle mitochondria, which could cause the production of free radicals and induce the myopathy. In this case, myopathy would not manifest with fluvastatin, but if the patient taking fluvastatin were also taking an NSAID (5% of our patients), especially the most frequent one, ibuprofen, he could also develop a myopathy.

5% of our patients were taking anti-hypertensive betablockers. Among the most used are metoprolol and carvedilol. If a patient taking metoprolol or carvedilol, due to a depressive process was also taking the most frequently prescribed antidepressants, i.e. fluoxetine or paroxetine (which are strong inhibitors of the liver enzyme CYP2D6 that eliminates metoprolol and carvedilol), in consequence a patient could manifest a 7-8 days long hypotension, that could even occur with loss of consciousness.

Pharmacogenetics

Completed in April 2003, the human genome project (HGP) gave us for the first time the ability to read

nature's complete genetic blueprint for building a human being. The HGP has revealed that there are probably about 20,500 human genes. Through the technology of genetic sequencing, we can determine single nucleotide polymorphisms (SNPs), which allows detecting changes in the DNA that may modify the activity of enzymes, transport proteins and therapeutic targets, the consequence of which would be an individual different response to the standard doses of some drugs.

The most known in pharmacogenetics is the SNPs that affects the pharmacokinetics of drugs. SNPs in the genes that encode hepatic enzymes such as P450, CYP1, CYP2 and CYP3, involved in drugs' elimination, may modify their pharmacokinetics, and therefore their blood levels. According to certain SNPs in the genotype, the enzymes may manifest a phenotype of normal activity (extensive metabolizers=EM), decreased activity, (intermediate metabolizers=IM), null almost activity greatly metabolizers=PM), or increased activity (ultrarapid metabolizers=UM). The standard dose of a drug according to the protocol, to a patient of EM phenotype will have the expected effects. But the same dose to a PM patient can cause toxic effects due to effective overdose, and in an UM patient can cause a therapeutic failure due to more rapid elimination than expected.

Therefore, to apply to all patients the same drug at the same dose "according to protocol", is to apply the "one size fits all", while we are genetically different, therefore we need a tailored medication according to our genes. A patient taking statins such as simvastatin or atorvastatin, and having a SNP in the SLCO1B1 gene that encodes the intestinal transport protein OATP1B1, would probably develop a myopathy within a few months. A patient taking the beta-blocker metoprolol and having a SNP in the CYP2D6 gene, whose phenotype is PM, would only eliminate 5-10% of the dose, so after five days he could have a hypotension crisis due to high levels of the drug.

In order to treat a patient correctly and minimise adverse effects as much as possible, we must apply pharmacogenetics and systematically consult, in appropriate databases, the interactions of the whole medication, without forgetting the herbs and other natural products that the patient takes by self-medication. Remembering "primum non nocere".

CONCLUSION

Medical care for elite vocal performers should provide a multidisciplinary approach and a comprehensive and integrated understanding of possible drug interactions and potential drugs' side effects. Regarding the voice quality, as crucial parameter, more studies should be performed about how particular medications may affect the proper function of the vocal cords. With no doubt, understanding the potential side effects of medications is extremely important for professional voice users, especially for

opera singers. Therefore, while administrating any drugs in this specific group of patients, the likelihood of benefit should be carefully considered and believed to be higher than the possibility of harm caused to the voice.

Funding: No funding sources Conflict of interest: None declared

Ethical approval: The study was approved by the

Institutional Ethics Committee

REFERENCES

- 1. Koufman JA, Isaacson G. The spectrum of vocal dysfunction. Otolaryngol Clin North Am. 1991;24:985-8.
- 2. Kwok M, Eslick GD. The impact of vocal and laryngeal pathologies among professional singers: a meta-analysis. J Voice. 2019;33(1):58-65.
- 3. Davies DG. Travel and the Vocal Performer. In: Care of the Professional Voice. London, United Kingdom: Butterworth Heinemann; 2004.
- Sataloff RT. Professional Voice: The Science and Art of Clinical Care. Fourth. Plural Publishing Inc. Available at: https://books.google.es/books/about/ Professional_Voice.htmlid=m6R3oAEACAAJ&redi resc=y. Accessed on 20 March 2019.
- Frare RG, Singh AK. A Critical Review of Physicochemical Properties and Analytical Methods Applied to Quantitative Determination of Ebastine. Vol 8347. Taylor and Francis; 2018.
- 6. Benninger MS, Murry T. The Performer's Voice. Plural Pub; 2006. Available at: https://books.google.es/books/about/The Performers Voice.htmlid = z 50e AQAAMAAJ &redir_esc=y. Accessed on 20 March 2019.
- 7. Abaza MM, Levy S, Hawkshaw MJ, Sataloff RT. Effects of medications on the voice. Otolaryngol Clin North Am. 2007;40:1081-90.
- 8. Nemr K, Di A, Silva C, Rodrigues DDA, Zenari MS, Paulo S. Medications and Adverse Voice Effects. J Voice. 2018;32(4):515.e29-39.
- 9. The world health report 2002: reducing risks, promoting healthy life. Geneva, World Health Organization; 2002.
- 10. Sataloff RT, Heman-ackah YD, Hawkshaw MJ. Clinical anatomy and physiology of the voice. Otolaryngol Clin North Am. 2007;40:909-29.
- 11. Reed Thompson A. Pharmacological agents with effects on voice. J Otolaryngol. 1995;16(1):12-8.
- 12. Empey PE. Pharmacogenomics to achieve precision medicine. Am J Heal Pharm. 2016;73(23):1906-7.
- 13. Goyal V, Gupta A, Gupta O, Lal D, Gill M. Comparative efficacy and safety of ebastine 20 mg, ebastine 10 mg and levocetirizine 5 mg in acute urticaria. J Clin Diagnostic Res. 2017;11(3):WC06-9.
- 14. Van Lierde KM, Claeys S, De Bodt M, Van Cauwenberge P. Response of the female vocal quality and resonance in professional voice users

- taking oral contraceptive pills: A multiparameter approach. Laryngoscope. 2006;116(10):1894-8.
- 15. Surow JB. "Alternative Medical Therapy" use among singers: prevalence and implications for the medical care of the singer. J Voice. 2000;14(3):398-409
- 16. Balch JF. Prescription for Natural Healing. 5th ed. Avery Trade; 2006.
- 17. Martin FG. Drugs and vocal function. J Voice. 1988;2(4):338-44.

Cite this article as: Clarós P, Mikolajczyk K, Pujol C, Pujol MC, Sabater J, Clarós A. Side effects of medications in professional opera singers' voice: survey findings. Int J Otorhinolaryngol Head Neck Surg 2020;6:213-23.

APPENDIX

Medication side effects survey

1.	Please, write down your initials:						
2.	What is your biological sex?: Female Male						
3.	What is your age?: yrs height?: cm weight?: kg						
4.	Do you smoke cigarettes?: Yes No						
	if yes how many per day, a	nd for how long?: _	/day for months/	years			
5.	How much alcohol do you		rarely a few times		daily		
6.	How many cups of fluids		•	-	•		
7.	What is your Tessitura (voice category)?:						
	Soprano Mezzo-Sopr		Tenor Baritone	Bass	Countertenor		
8.	Are you?: Active Perform						
9. What are your allergies (answer if you have any)?:							
	Dust Mold Trees C			er:			
10.	*[For female only] How w	U					
	Premenopause (before m						
	Menopause		-8 F 1				
	Postmenopause (after me	enonause)					
11.	Do you have any chronic	_					
	•				 e how much do you take per		
14.	day and for how long?:	tutale every day	picuse give the nume(s)	una wiii	e now much do you take per		
	Name	Dosage	How long				
	Tume	(mg)	-				
		(mg)	months/years				
		(mg)	months/years				
		(mg)	months/years				
	 	=	months/years				
		(mg)	months/years				
12	Have you ever noticed an	(mg)	<u> </u>	ation			
13.	if yes, please give a name(s			ation,			
	Name of a drug	Side effect(S)	ide effect(s)?.	Severity[0-10] Onset		
	Name of a drug	side effect(s)		Severity			
					Beginning/Later		
					Beginning/Later		
		-			Beginning/Later Beginning/Later		
					•		
					Beginning/Later		
	[How severe was this symp				Beginning/Later		
			• -	ontho/read	ma?) of atomting talking it?]		
11	Does this side effect occur Does taking this drug(s) a		Later (after now many m	onuis/yea	is?) of starting taking it?]		
14,	(in case of more than one n	•	wite derrin the nemes nee	a tha arm	mtomo)		
		-	The down the names nea	r the sym	ptoms)		
	Hoarseness (coarse or stratchy sound)Fatigue (voice tires or changes quality after speaking for a short period of time)						
	Volume disturbance (trouble of speaking) soflty, loudly						
	Loss of range (high, low)					
	Vocal tremor						
	Changes in fiatto	, , , , ,	1.6	`			
	Change in classification			ezzo)			
	Prolonged warm- up tim	e (over 1/2 hour to v	warm up)				
	Breathiness						
	Frequently clearing your	throat					

	Tickling sensation w	hile speaking or fo	reign body sensation in the larynx	
	Pain in throat while s	peaking.		
	Bitter or acid taste- b	ad breath		
	other way:			
15.	What types of medicat	tion(s) do you tak	e from time to time (occasionally)	?:
	[including drugs withou	out prescription-O7	CC (over-the-counter medications) l	ike Paracetamol, anti-inflammatory
	drugs (ibuprofen etc.),h	erbal products, vita	amins, diet supplements)	•
	(please give the name(s), the dosage, side	effects and severity):	
	Name	Dosage	Side effect(s)	Severity[0-10]
		(mg)		
16.	Do you check routinel	y the composition	of the medications, herbals or vi	tamins which you can buy withou
	prescription?: Yes	No		-