Table I. Clinical and demographic features of patients diagnosed with nodular melanoma and melanoma—other

	Nodular melanoma (n = 60)	Melanoma—other (n = 265)	*P* value
Men, %	98.0	96.9	.65
Race, white, %	94.9	94.8	.97
Average age, y	70	67	.03
Average Breslow thickness, mm	3.9*	0.76	<.01
Lesion identified by patient, %	38.5	22.2	.01
VA primary care physician visit in preceding 6 months, %	85.0	92.9	.05
VA dermatology visit in preceding 6 months, %	20.0	34.2	.03
Age-appropriate colonoscopy screening, %	47.0	73.7	<.01
History of skin cancer, %	38.9	51.3	.08
History of other noncutaneous malignancy, %	20.0	34.0	.04

VA, Veterans Affairs.
*Seen by dermatology in preceding 6 months: yes, 1.81 mm; no, 3.85 mm ($P = .006$).

evaluate barriers to care in this and the general population.

Another key finding of the present study is that routine visit to a dermatologist is associated with early detection of NMs at a more survivable stage of <2 mm.[2] A previous study also found that individuals who had a skin check in the past 3 years had thinner NMs.[3] Individuals with thinner NMs are also more likely to report "change in color" and "irregular shape" in their NMs.[3] Taken together, these results suggest that close contact with a dermatologist may result in both institutional-based protective factors (eg, prompt detection by obtaining a biopsy specimen) and individual-based protective factors (eg, routine at-home self-examination and attentiveness to melanoma-specific signs) that can be lifesaving.

Routine contact with a dermatologist can be lifesaving for individuals who are at risk for NM. The results of the present study emphasize the importance of preventative care.

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Funding sources: None.

Conflicts of interest: None disclosed.

The Institutional Review Board at Veterans Affairs Miami Health Care System approved this study (protocol 4987.04). Presented in abstract form at the American Academy of Dermatology Annual Meeting, March 3-7, 2017, Orlando, Florida.

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https://doi.org/10.1016/j.jaad.2018.10.012

Effect of postinjection facial exercise on time of onset of botulinum toxin for glabella and forehead wrinkles: A randomized, controlled, crossover clinical trial

To the Editor: Many clinicians recommend exercising treated muscles for 4 hours after botulinum toxin injection in order to enhance cellular uptake; however, no data exist in the literature to substantiate the physiology or the clinical efficacy of this method.[1] The purpose of this study was to determine whether facial muscle exercises after injection of botulinum toxin into forehead and glabella rhytids results in

Table I. Blinded dermatologists' photoratings of glabella and forehead wrinkles at rest and action contraction over time

Time after botulinum toxin, days	Treatment arm	Glabella				Forehead			
		Static		Dynamic		Static		Dynamic	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
0	No muscle contraction	0.727	0.63	2.091	0.68	1.318	0.84	2.500	1.01
	Active muscle contraction	0.591	0.59	2.045	0.72	0.955	0.58	2.364	0.90
	P value	.38		1.00		.03		.58	
1	No muscle contraction	0.571	0.51	1.762	0.89	0.905	0.70	1.952	0.86
	Active muscle contraction	0.500	0.51	1.636	0.79	0.864	0.56	2.045	0.90
	P value	.50		.63		1.00		.62	
2	No muscle contraction	0.455	0.51	1.500	0.67	0.905	0.53	1.364	0.66
	Active muscle contraction	0.455	0.51	1.182	0.85	0.727	0.63	1.591	0.67
	P value	1.00		.12		.22		.26	
3	No muscle contraction	0.591	0.59	1.545	0.67	0.905	0.54	1.476	0.60
	Active muscle contraction	0.524	0.60	0.857	0.65	0.571	0.51	1.333	0.48
	P value	.63		.002		.02		.50	
4	No muscle contraction	0.167	0.38	1.000	0.69	0.500	0.51	1.222	0.65
	Active muscle contraction	0.318	0.48	0.727	0.70	0.545	0.51	1.273	0.70
	P value	1.00		.11		1.00		1.00	
7	No muscle contraction	0.333	0.58	0.857	0.65	0.524	0.51	1.143	0.65
	Active muscle contraction	0.400	0.60	0.550	0.69	0.350	0.49	0.950	0.51
	P value	.63		.11		.73		.45	
14	No muscle contraction	0.227	0.43	0.409	0.59	0.409	0.59	0.955	0.65
	Active muscle contraction	0.227	0.43	0.455	0.51	0.227	0.43	0.864	0.64
	P value	1.00		1.00		.22		.75	

SD, Standard deviation.

more rapid improvement in wrinkle appearance than injections without exercise.

Eligible participants were women who were 18 to 65 years of age and were in good health with dynamic rhytids of the forehead and glabella who were recruited from an urban hospital-based dermatology practice. Participants were randomized to either perform a prescribed facial exercise regimen (3 sets, separated by 10 minutes, of 40 forehead raises followed by 40 scowls, or knitting of the brows) or to refrain from facial contractions for 4 hours after toxin injections. Two blinded dermatologist photoraters assessed forehead and glabella dynamic creases at baseline and on days 1, 2, 3, 4, 7, and 14 using the 5-point Carruthers' forehead lines dynamic grading scale and 4-point Gladys rating scale for glabellar frown lines. Each participant also live-assessed their own dynamic creases using a 7-point subject self-evaluation improvement Scale (−3 to +3). At 7 months, participants were crossed over to the other arm.

Of the 25 women who consented and enrolled, 22 participants with a mean age of 46.7 years (range 27-66 years) completed the study per protocol. Both dermatologists and participants rated dynamic glabellar and static forehead wrinkles to be significantly better by day 3 when injections were followed by facial contractions (dermatologists' ratings $P = .002$ and $P = .02$, respectively; participants' ratings $P = .01$ and $P = .02$, respectively; Tables I and II). Participants also reported noticeable glabellar improvement by days 2 and 3 when injections were followed by facial exercise compared with days 3 and 4 without exercise ($P = .02$). A significant advantage in the exercise group was detectable as early as day 3, at which point patients' self-evaluation wrinkle scores increased by approximately twice as much in exercisers compared with nonexercisers. However, the overall degree of effect was the same in both exercise and nonexercise arms at 14 days, and the duration of action also did not appear to differ between the 2 arms.

In general, the facial exercise regimen was well-tolerated by participants; 59% of participants reported that muscle contractions were very easy to perform. Sixty-eight percent believed that contractions sped the onset of action and increased toxin efficiency but did not impact duration of effectiveness.

The results of this study suggest that a postinjection facial exercise regimen is a safe and effective method for achieving an earlier onset of clinical effect of botulinum toxin injections.

Table II. Patient self-evaluation of glabella and forehead wrinkle improvement over time

Time after botulinum toxin, days	Treatment arm	Glabella		Forehead	
		Mean	SD	Mean	SD
1	No muscle contraction	0.773	0.87	0.591	0.59
	Active muscle contraction	0.682	0.65	0.636	0.58
	P value	.83		.98	
2	No muscle contraction	0.864	0.89	0.864	0.71
	Active muscle contraction	1.409	0.73	1.182	0.66
	P value	.02		.21	
3	No muscle contraction	1.273	0.88	1.455	0.80
	Active muscle contraction	1.810	0.68	1.857	0.57
	P value	.01		.02	
4	No muscle contraction	1.500	1.14	1.773	0.81
	Active muscle contraction	2.000	0.62	2.136	0.47
	P value	.13		.08	
7	No muscle contraction	2.091	0.97	2.136	1.08
	Active muscle contraction	2.286	0.72	2.381	0.50
	P value	.67		.53	
14	No muscle contraction	2.045	1.13	2.455	0.74
	Active muscle contraction	2.455	0.67	2.591	0.50
	P value	.16		.53	
90	No muscle contraction	1.727	0.91	1.818	0.98
	Active muscle contraction	1.455	1.03	1.318	1.14
	P value	.61		.87	

SD, Standard deviation.

Expediting the time to noticeable benefit, even by 1 day, may be clinically significant for some patients.[2,3] To avoid needless inconvenience, exercise could be recommended only for those who desire more rapid results. To precisely delineate the time of exercise-mediated onset, a future study might measure contractions every 12 hours, especially considering that toxin binding to cholinergic receptor sites is complete by 64 minutes postinjection.[1,4,5] Future studies may include men, other neuromodulators, different injection sites, and different exercise regimens to determine minimal needs.

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Supported by departmental research funds of the Department of Dermatology, Northwestern University.

Dr Alam has received royalties from Elsevier for technical books he has edited and has a consulting relationship with Pulse Biosciences (both <$5000 per year). The other authors have no conflicts of interest to declare.

Reviewed and approved by the Northwestern University Institutional Review Board (STU00056722). Clinicaltrials.gov listing: NCT01689012.

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https://doi.org/10.1016/j.jaad.2018.10.013

Lack of evidence for feminization of males exposed to spironolactone in utero: A systematic review

To the Editor: Because of its antiandrogen properties, spironolactone is accepted and used as a therapeutic option for hormonal acne. Its risk in women of childbearing potential is conflicting. While it has been shown to cause feminization of male animals exposed in utero, it is also approved by the US Food and Drug Administration to treat edema in pregnant women (25-200 mg/day).[1]

To help dermatologists understand the risks of spironolactone use in pregnancy, we performed a qualitative systematic review to identify cases of male animals and humans exposed to spironolactone in utero.

In May 2018, a search in the PubMed database using the terms "spironolactone," "human/male/boy/mouse/mice/rat/rabbit/animal," and "pregnancy/in utero" generated 178 unique results. Manuscripts were included in our final analysis if male subjects were exposed to spironolactone during the human- or animal-specific period of genital development, and if they described the final development of the exposed offspring. Of these publications, 8 met the criteria, and they were combined with 5 animal studies reported in the spironolactone product insert.

Using US Food and Drug Administration guidelines, doses in animals were converted to equivalent daily human doses by body surface area, which accounts for variations in metabolism and drug distribution.[2]

Feminization of exposed males was observed in 6 of 9 animal studies (Table I). Of these, 5 studies used dosing greater than the human equivalent of 200 mg per day. The severity of genital dysmorphism in male animals was often dose dependent.

In humans, 5 males were born to mothers with renal disease who were treated with spironolactone before and during their pregnancies (Table II). There was no evidence of feminization despite exposure to doses as high as 400 mg a day. One of these boys was re-examined at puberty and was noted to have appropriate genital development.

We found 1 report of a male born with ambiguous genitals who was exposed to spironolactone until week 5.[11] However, the medication was stopped before genital development started, and spironolactone has a half-life of <17 hours.[1]

In the reviewed data, spironolactone at doses greater than the human equivalent of 200 mg daily caused feminization of male animal offspring, while doses <100 mg did not. Between these doses, the data are mixed.

In humans, genital differentiation starts at week 6 and is complete by weeks 12 to 14.[12] Because most women do not realize they are pregnant until gestational week 6,[13] it is likely that many male fetuses have been exposed to spironolactone while undergoing genital differentiation. Although we

Table I. Studies of animals exposed to spironolactone in utero

Study subject	Study no.	Maximum daily dose	Equivalent human dose,* mg	Results	Reference
Mouse					
	1	20 mg/kg	97.6	No feminization of offspring observed	Aldactone insert[1]
Rabbit					
	1	20 mg/kg	387	Feminization of male offspring	Aldactone insert[1]
Rat					
	1	40 mg	2581	Feminization of male offspring	Hecker et al[3]
	2	200 mg/kg	1935	Feminization of male offspring	Aldactone insert[1]
	3	20 mg	1296	Feminization of male offspring	Jaussa et al[4]
	4	100 mg/kg	972	Feminization of male offspring	Aldactone insert[1]
	5	20 mg/kg	194	Feminization of male offspring	Aldactone insert[1]
	6	20 mg/kg	194	Normal development of all organs	Seassaro et al[5]
	7	6 mg/kg	58	No feminization of offspring observed	Rose et al[6]

*By body surface area.