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Letters to the Editor

Isotretinoin: reasserting its public health value at the population level, addressing potential neuropsychiatric risk at the individual level

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Linked Articles: Paljarvi *et al. Br J Dermatol* 2022; **187**:64–72; Ravencroft and Eichenfield. *Br J Dermatol* 2022; **187**:8–9.

Dear Editor, We read with interest the study evaluating the risk of severe neuropsychiatric outcomes in a population with acne using isotretinoin and its related commentary.[1,2] The authors used a propensity-matched cohort of electronic medical records, including a large population of patients with acne exposed to isotretinoin (30 866) compared with several controls, including patients with acne with oral antibiotics, topical treatments or no treatment at all. Considering the most important studies on this topic, the evidence *at the population level* is as follows:

(i) isotretinoin is the drug of choice in severe acne, decreasing the risk of sequelae;[3,4]

(ii) the risk of suicide is higher in a population with acne than in a matched population without acne (odds ratio 1.46 in the latter study);[1,5]

(iii) the great majority of studies did not demonstrate an excess risk of severe neuropsychiatric events in patients with acne exposed to isotretinoin; and

(iv) isotretinoin-treated patients with acne have less neuropsychiatric risk than those untreated or treated with antibiotics (odds ratio 0.80 in the latter study).[1,6]

In parallel, some case reports in the medical literature have highlighted the risk of depression and mood disorders in isotretinoin-exposed patients with challenge, dechallenge and rechallenge occurrences. Extremely rare suicides were also reported – including in the general media; each story is an absolute tragedy pointing to the potential neuropsychiatric risk of isotretinoin at the individual level. Clinicians, scientists, regulators and patients should agree that these data are not in the least contradictory. In fact, they indicate that (i) at the population level, the benefit-to-risk ratio of isotretinoin still allows for its approval or recommendation in severe acne, in the hope of better controlling the disease and subsequent morbidities, such as scars and psychosocial distress; and (ii) at the individual level, an idiosyncratic risk of severe neuropsychiatric events exists, including in patients presenting without any psychological symptoms at prescription, therefore making excellent patient information and strict surveillance necessary.

Potentially vulnerable patients are not easily identifiable and pharmacogenomics may provide clues. At present, the use of the Adolescent Depression Rating Scale by both dermatologists and patients may help to detect high-risk patients and stop isotretinoin early enough to avoid severe outcomes. However, only a pilot study has been published in acne,[7] and more experience and information, to be gathered during office-based standard consultations, including on a monthly basis, are required. Recognizing the importance of isotretinoin in dermatology, dermatologists, scientists and regulators should continue to provide data, tools and clues to help increase both the efficacy and safety of isotretinoin prescription in our patients.

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References

1 Paljarvi T, McPherson T, Luciano S *et al.* Isotretinoin and adverse neuropsychiatric outcomes: retrospective cohort study using routine data. *Br J Dermatol* 2022; **187**:64–72.

2 Ravencroft J, Eichenfield L. Isotretinoin does not contribute to increased neuropsychiatric risk in the overall acne population, but risk management during treatment remains essential. *Br J Dermatol* 2022; **187**:8–9.
3 Société Française de Dermatologie. Recommandations Acné. Available at: https://reco.sfdermato.org/fr/recommandations-acné (last accessed 12 July 2022).
4 National Institute for Health and Care Excellence. Acne vulgaris: management. Available at: https://www.nice.org.uk/guidance/ng198 (last accessed 12 July 2022).
5 Halvorsen JA, Stern RS, Dalgard F *et al.* Suicidal ideation, mental health problems, and social impairment are increased in adolescents with acne: a population-based study. *J Invest Dermatol* 2011; **131**:363–70.
6 Droitcourt C, Nowak E, Rault C *et al.* Risk of suicide attempt associated with isotretinoin: a nationwide cohort and nested case-time-control study. *Int J Epidemiol* 2019; **48**:1623–35.
7 Hefez L, Micallef J, Revah-Levy A *et al.* First use of the Adolescent Depression Rating Scale (ADRS) in the management of young people with severe acne treated with isotretinoin: a pilot study of an active monitoring of depressive disorders by dermatologists. *Clin Exp Dermatol* 2022; **47**:709–16.

Response to 'British Association of Dermatologists guidelines for the management of adults with basal cell carcinoma 2021': vismodegib and indications for its use

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Dear Editor, The latest British Association of Dermatologists guidelines[1] for the management of basal cell carcinoma (BCC) have once again established a robust framework, highlighting advances in the management of the most common skin cancer in the UK. Inclusion of the novel biologic drug vismodegib offers a unique opportunity for a subgroup of the population who have developed 'advanced BCC' and for patients with the genodermatosis Gorlin syndrome.[1] Treatment options for locally advanced BCC (laBCC) and metastatic BCC (mBCC) include surgery, radiotherapy and, in rare selected cases, cytotoxic chemotherapy. When these options are not appropriate, best supportive care is advised. Up until its withdrawal from the Cancer Drugs Fund (CDF) in 2017,[2] vismodegib offered a hopeful therapeutic option for these patients. Recommendation 14 of the new guidelines offers vismodegib 'as a treatment option to adults with advanced BCC who are unsuitable for Mohs micrographic surgery, standard surgical excision or radiotherapy, including patients with Gorlin syndrome, following discussion at an MDT (multidisciplinary team).'[1] Unfortunately, vismodegib does not have National Institute for Health and Care Excellence (NICE) or CDF approval for these indications. In view of this, we feel the guidelines should provide further clarification on the use of this novel drug.

Currently NICE (TA 489) does not recommend the use of vismodegib within its licensed indications, for laBCC and mBCC that are inappropriate for surgery or radiotherapy.[3] This has been attributed to uncertainty of evidence when comparing vismodegib with best supportive care and lack of cost-effectiveness.[3] However, the CDF still funds vismodegib within the National Health Service (NHS) for a limited range of indications.[4] The inclusion criteria (Table 1) must be satisfied at each of the 14 given points, for patients to be eligible for vismodegib. Briefly, patients who are considered for treatment must have either Gorlin or non-Gorlin related nonlocally advanced nonmetastatic BCCs. At least six operable lesions must be present and three lesions must be of ≥ 5 mm in diameter. In non-Gorlin multiple BCC, these lesions must be appropriate for surgery. Of the above conditions, at least one BCC must have histopathologic confirmation and while eligible patients must be suitable for surgical intervention, it must be considered that surgery may result in 'substantial disfigurement'. Patients must be over 18 years of age, appropriately counselled on the teratogenic properties of vismodegib and involved in a discussion with a skin specialist or head and neck MDT. This approach has been supported by NHS England, who recommend the routine commissioning of vismodegib in line with the above criteria.[2]

Despite the lack of support by NICE, funding is available for the limited indications outlined by the CDF. Therefore, while vismodegib may represent an effective treatment option

Table 1 A limited summary of the criteria for the consideration of vismodegib

Inclusion	The patient has either:	Minimum six lesions with at least three lesions ≥ 5 mm
	1 Gorlin syndrome with nonlocally advanced, nonmetastatic BCC	Minimum six lesions with at least three lesions ≥ 5 mm and appropriate for surgery
	2 Non-Gorlin-related nonlocally advanced, nonmetastatic BCC	At least three lesions ≥ 5 mm and at least one lesion with histopathologic confirmation
	At least six operable nonlocally advanced, nonmetastatic BCCs	
	Where surgery alone may cause 'substantial' disfigurement	
	Patient has been assessed and vismodegib recommended by a skin cancer specialist or head and neck multidisciplinary team	
	Eastern Cooperative Oncology Group performance status 0, 1 or 2	
Exclusion	Patients below the age of 18 years	
	Pregnancy	

BCC, basal cell carcinoma. Table adapted from National Cancer Drug Fund list.[4] Available at: https://www.england.nhs.uk/cancer/cdf/cancer-drugs-fund-list/.