



West Middlesex University Hospital

**Date of Search: 23/06/2016**

**Sources Searched: Medline, Embase, DynaMed**

### **Pharmacokinetics of Methyldopa**

#### **Absorption:**

#### **Bioavailability:**

Generally about 50% of an oral dose is absorbed with peak plasma concentrations usually attained in approximately 3–6 hours. <sup>b</sup>

#### **Onset:**

Following oral administration, maximum decrease in BP occurs in 4–6 hours. <sup>b c</sup>

Following IV administration, BP begins to decrease in 4–6 hours. <sup>b f</sup>

#### **Duration:**

Following discontinuance of oral therapy, BP returns to pretreatment levels within 24–48 hours. <sup>e</sup>

Following IV administration, hypotensive effect lasts for 10–16 hours and hypertension recurs within 48 hours. <sup>b f</sup>

#### **Distribution:**

#### **Extent:**

Crosses the blood-brain barrier. <sup>h i</sup>

Methyldopa crosses the placenta in humans <sup>101 102</sup> and is distributed into milk. <sup>101 103</sup>

**Source:** American Society of Health System Pharmacists, Inc., DynaMed [Internet]. Ipswich (MA): EBSCO Information Services. 1995 - . Record No. 233114, Methyldopa; [updated 2016 Jan 29, cited **23/06/2016**]; [about 9 screens]. Available from <http://web.a.ebscohost.com/dynamed/detail?vid=2&sid=bb2acd63-2ad8-4a40-9d2e-47f02dc78357%40sessionmgr4001&hid=4107&bdata=JnNpdGU9ZHluYW1lZC1saXZlJnNjb3BIPXNpdGU%3d#AN=233114&db=dme>

### Search History:

1. PsycInfo; exp METHYLDOPA/; 56 results.
2. PsycInfo; METHYLDOPA.ti,ab; 118 results.
3. PsycInfo; 1 OR 2; 127 results.
4. PsycInfo; depress\*.ti,ab; 242576 results.
5. PsycInfo; exp MAJOR DEPRESSION/; 106868 results.
6. PsycInfo; 4 OR 5; 247196 results.
7. PsycInfo; 3 AND 6; 23 results.
8. EMBASE; \*METHYLDOPA/; 5509 results.
9. EMBASE; METHYLDOPA.ti; 1293 results.
10. EMBASE; 8 OR 9; 5639 results.
11. EMBASE; exp DOSE TIME EFFECT RELATION/; 30800 results.
12. EMBASE; exp DRUG MECHANISM/; 282202 results.
13. EMBASE; 10 AND 11 AND 12; 1 results.
14. EMBASE; "Onset of action".ti,ab; 5147 results.
15. EMBASE; 10 AND 14; 4 results.
16. EMBASE; \*PHARMACODYNAMICS/; 5504 results.
17. EMBASE; 10 AND 16; 11 results.
18. EMBASE; (onset adj2 "side effect\*").ti,ab; 171 results.
19. EMBASE; 10 AND 18; 0 results.
20. EMBASE; exp METHYLDOPA/; 12358 results.
21. EMBASE; 14 AND 20; 12 results.
22. EMBASE; exp TIME/; 499750 results.
23. EMBASE; 10 AND 22; 66 results.
24. EMBASE; exp DRUG METABOLISM/; 143756 results.
25. EMBASE; 10 AND 24; 147 results.
26. EMBASE; exp MOOD DISORDER/; 393275 results.
27. EMBASE; 10 AND 26; 134 results.
28. EMBASE; exp DRUG MECHANISM/; 282202 results.
29. EMBASE; 20 AND 22 AND 28; 1 results.
30. EMBASE; exp PREGNANCY/; 619800 results.
31. EMBASE; 10 AND 28 AND 30; 2 results.
32. EMBASE; 10 AND 30; 398 results.
33. EMBASE; exp LIVER ENZYME/; 21958 results.
34. EMBASE; 32 AND 33; 0 results.
35. EMBASE; 32 AND 33; 0 results.
36. EMBASE; exp LIVER TOXICITY/ OR exp TOXIC HEPATITIS/; 72319 results.
37. EMBASE; 32 AND 36; 9 results.
38. EMBASE; exp DEPRESSION/; 360230 results.
39. EMBASE; 20 AND 30 AND 38; 44 results.
40. EMBASE; exp PREECLAMPSIA/; 43381 results.
41. EMBASE; 38 AND 40; 397 results.
42. EMBASE; 20 AND 41; 34 results.
43. EMBASE; exp PUERPERAL DEPRESSION/; 7518 results.

44. EMBASE; 10 AND 43; 0 results.
45. EMBASE; 20 AND 43; 10 results.
46. EMBASE; exp MATERNAL HYPERTENSION/; 12432 results.
47. EMBASE; 20 AND 38 AND 46; 41 results.
48. Medline; exp METHYLDOPA/; 5632 results.
49. Medline; METHYLDOPA.ti,ab; 2640 results.
50. Medline; 48 OR 49; 6494 results.
51. Medline; "Onset of action".ti,ab; 3554 results.
52. Medline; 50 AND 51; 6 results.
53. Medline; "mechanism of action".ti,ab; 55815 results.
54. Medline; 50 AND 53; 41 results.
55. Medline; PHARMACODYNAMICS.ti,ab; 13320 results.
56. Medline; 50 AND 55; 21 results.
57. Medline; DOSE-RESPONSE RELATIONSHIP, DRUG/; 357448 results.
58. Medline; 50 AND 57; 375 results.
59. Medline; 49 AND 57; 116 results.
60. Medline; hepatitis.ti,ab; 178394 results.
61. Medline; exp HEPATITIS/; 143878 results.
62. Medline; exp DEPRESSION/ OR exp DEPRESSION, POSTPARTUM/; 91023 results.
63. Medline; depression.ti,ab; 245610 results.
64. Medline; exp MOOD DISORDERS/; 101092 results.
65. Medline; 60 OR 61 OR 62 OR 63 OR 64; 518547 results.
66. Medline; pregn\*.ti,ab; 404033 results.
67. Medline; exp PREGNANCY/; 787537 results.
68. Medline; 66 OR 67; 869784 results.
69. Medline; 50 AND 65 AND 68; 11 results.
70. Medline; exp TIME FACTORS/; 1057757 results.
71. Medline; 50 AND 68 AND 70; 18 results.
72. EMBASE; exp SLOW RELEASE FORMULATION/; 1339 results.
73. EMBASE; 10 AND 72; 0 results.
74. EMBASE; slow.ti,ab; 200133 results.
75. EMBASE; 10 AND 74; 33 results.
76. EMBASE; DRUG RESPONSE/; 118886 results.
77. EMBASE; 10 AND 76; 78 results.
78. Medline; (onset adj2 "side effect\*").ti,ab; 223 results.
79. Medline; 50 AND 78; 0 results.
80. Medline; "slow acting".ti,ab; 731 results.
81. Medline; 50 AND 80; 0 results.
82. Medline; 50 AND 80; 0 results.
83. EMBASE; \*DRUG MECHANISM/; 38669 results.
84. EMBASE; 10 AND 83; 79 results.
85. EMBASE; \*DRUG EFFECT/; 7119 results.
86. EMBASE; 10 AND 85; 1 results.

---

**Title:** How to assess and manage hypertension during and after pregnancy

**Citation:** Clinical Practice, July 2013, vol./is. 10/4(455-470), 2044-9038;2044-9046 (July 2013)

**Author(s):** McKenna L.A., Huda S.S., Freeman D.J., Jarvie E.

**Language:** English

**Abstract:** Hypertensive disorders of pregnancy are increasingly important complications of which clinicians should have an up-to-date knowledge to facilitate prompt recognition, diagnosis and management. These disorders affect a growing number of pregnancies worldwide, with incidence rates likely to increase in the future commensurate with increasing maternal age and maternal comorbidities independent of age, with consequent effects on maternal and fetal/neonatal morbidity and mortality rates. This article mainly focuses on management within the UK of these disorders, examining their current working definitions, detection methods and recent developments in screening tool development. The current NICE-recommended strategies for treating these disorders and minimizing their occurrence in pregnancy are also explored. In addition, the association between adverse pregnancy outcome and increased risk of future maternal and offspring cardiovascular disease is described, with comments on future strategies to help minimize these potential risks. © 2013 Future Medicine Ltd.

**Publication Type:** Journal: Review

**Source:** EMBASE

**Full Text:**

Available from *ProQuest* in [Clinical Practice](#)

---

**Title:** Methyldopa

**Citation:** Practical Diabetes International, May 2010, vol./is. 27/4(166-167), 1357-8170;1528-252X (May 2010)

**Author(s):** Iliodromiti S., Mackenzie F., Lindsay R.S.

**Language:** English

**Publication Type:** Journal: Article

**Source:** EMBASE

**Full Text:**

Available from *John Wiley and Sons* in [Practical Diabetes International](#)

Available from *John Wiley and Sons* in [Practical Diabetes International](#)

---

**Title:** Clinical management of hypertension in pregnancy

**Citation:** High Blood Pressure and Cardiovascular Prevention, 2013, vol./is. 20/3(123-127), 1120-9879;1179-1985 (2013)

**Author(s):** Borghi C., Ferri C., Sechi L.

**Language:** English

**Publication Type:** Journal: Article

**Source:** EMBASE

**Full Text:**

Available from *ProQuest* in [High Blood Pressure and Cardiovascular Prevention](#)

---

**Title:**  $\alpha$ -Methyldopa-induced hepatitis during the postpartum period.

**Citation:** BMJ case reports, Jan 2014, vol. 2014, 1757-790X (2014)

**Author(s):** Kashkooli, Soleiman, Baraty, Brandon, Kalantar, Jamshid

**Abstract:** A 34-year-old woman, with a history of pre-eclampsia, was diagnosed with  $\alpha$ -methyldopa-induced hepatotoxicity, after she presented with severe jaundice and hepatitis 8 weeks following delivery. Laboratory investigations and liver biopsy ruled out other causes of hepatitis. She continued to improve clinically after cessation of  $\alpha$ -methyldopa, and was discharged 10 days after admission. This case report emphasises that it may not be possible to predict which patients may develop  $\alpha$ -methyldopa-induced hepatitis, hence regular monitoring of liver function tests during treatment should be implemented.

**Source:** Medline

**Full Text:**

Available from *Highwire Press* in [BMJ Case Reports](#)

Available from *National Library of Medicine* in [BMJ Case Reports](#)

---

**Title:** Hepatotoxicity of alpha-methyldopa in pregnancy

**Citation:** Journal of Clinical Pharmacy and Therapeutics, June 2010, vol./is. 35/3(361-363), 0269-4727;1365-2710 (June 2010)

**Author(s):** Slim R., Salem C.B., Hmouda H., Bouraoui K.

**Language:** English

**Abstract:** Alpha-methyldopa is one of the most widely prescribed antihypertensive agents used during pregnancy. Despite its known potential hepatotoxicity, there have been only a few reports describing hepatotoxicity with the use of this drug during pregnancy. We report here a new case of acute hepatitis in a pregnant woman related to the use of alpha-methyldopa, and briefly review the literature on alpha-methyldopa-induced hepatotoxicity in pregnancy. © 2010 Blackwell Publishing Ltd.

**Publication Type:** Journal: Article

**Source:** EMBASE

**Full Text:**

Available from *Wiley* in [Journal of Clinical Pharmacy and Therapeutics](#)

Available from *EBSCOhost* in [Journal of Clinical Pharmacy & Therapeutics](#)

Available from *Wiley* in [Journal of Clinical Pharmacy and Therapeutics](#)

---

**Title:** [Methyldopa-induced acute reactive hepatitis in pregnancy, drug-metabolizing capacity of the liver].

**Citation:** Orvosi hetilap, Mar 2010, vol. 151, no. 11, p. 457-461, 0030-6002 (March 14, 2010)

**Author(s):** Ozsvár, Zsófia, Solymossi, Zsuzsa, Monostory, Katalin

**Abstract:** Alpha-methyldopa is a regularly used antihypertensive drug during pregnancy. Methyldopa, which decreases the sympathoadrenal system, is the first drug of choice since decades. The reactive hepatitis is not frequent, but known serious side effect of alpha-methyldopa. In non-pregnant women the estimated rate of manifest hepatotoxicity is 2.5-10%. In our case, gestation hypertension developed at the 21st gestation week of a 35 year-old pregnant woman. Oral methyldopa, a central alpha adrenergic blocker therapy was introduced. On the 23rd gestation week acute hepatitis developed. During differential diagnosis of hepatitis, the etiology of methyldopa was taken into account. Viral and autoimmune origin was ruled out. No fetal aberration was found during ultrasound examination. The function of drug metabolizing function from blood was measured by CYP phenotyping (CYP gene expression analysis). CYP3A4 enzyme plays a primary role in the metabolism of nifedipine. Antihypertensive therapy was changed from methyldopa to nifedipine. Nifedipine dosage was based on the value of CYP3A4 gene expression. With the reduced nifedipine therapy (30 mg daily), blood pressure was successfully under control. The diagnosis of alpha-methyldopa induced hepatitis was based on anamnesis, clinical picture and the results of chemical and radiological examination and confirmed by the level of drug-metabolizing capacity. The gestation hepatotoxicity of alpha-methyldopa was reported first in 1969 by Elkington Smith, who suggested the monitoring of serum aminotransferase during alpha-methyldopa therapy in pregnancy in their case report. Our case report confirms that monitoring of serum aminotransferase level is still valuable when treating a pregnant woman with alpha-methyldopa.

**Source:** Medline

---

**Title:** Alpha-methyldopa hepatotoxicity in pregnancy.

**Citation:** Journal of the College of Physicians and Surgeons--Pakistan : JCPSP, Feb 2009, vol. 19, no. 2, p. 125-126, 1022-386X (February 2009)

**Author(s):** Ali, Tauseef, Srinivasan, Nandakumar, Le, Vu, Rizvi, Syed

**Abstract:** A 12-week pregnant, 33-year-old African American female, presented with jaundice and change in urine colour. Liver function tests revealed raised transamines and normal alkaline phosphatase. She was started on methyldopa 6 weeks prior to presentation. After initial negative investigations including viral and autoimmune hepatitis, she was given prednisone for methyldopa induced hepatitis. Two weeks later, repeat enzymes revealed normal values. Important clinical and management points related to methyldopa induced hepatotoxicity are discussed.

**Source:** Medline

---

**Title:** Antihypertensives in hypertensive disorders of pregnancy

**Citation:** Bangladesh Journal of Obstetrics and Gynecology, September 2008, vol./is. 23/2(65-72), 1018-4287 (September 2008)

**Author(s):** Begum F., Parveen T.

**Language:** English

**Abstract:** Hypertension is the most common medical disorder in pregnancy. It complicates about 15% of all pregnancies and is an important cause of maternal and foetal morbidity and mortality. Hypertension is diagnosed from an absolute rise in blood pressure at or above 140/90 mm of Hg. There is general consensus that severe hypertension should receive pharmacological treatment but the value of treating mild hypertension is controversial. The threshold for treatment is 140-150 mm of Hg systolic and/ or 95-100 mm of Hg diastolic to prevent worsening complications of hypertensive mother. Opinions differ as to which is the best antihypertensive during pregnancy. All antihypertensives are either shown or assumed to cross the placenta and reach foetal circulation. While the goal of treatment is to reduce maternal risk, agents selected must be efficacious and safe for the foetus. Methyldopa and labetalol are considered as the first line antihypertensives. As second line therapy, calcium channel blocker, oral hydralazine are recommended. As third line agent, beta-adrenergic blockers are used. For immediate lowering of blood pressure sublingual Nifedipine, parenteral or oral Labetolol, parenteral Hydralazine are used. Atenolol use should probably be avoided in pregnancy because of its association with low birth weight. Both Angiotensin converting enzymes and Angiotensin receptor blockers are fetotoxic and contraindicated during pregnancy. This review article was done with the aim

to update knowledge regarding indication, safety, side effects as well as impact of anti-hypertensives on the foetus.

**Publication Type:** Journal: Review

**Source:** EMBASE

**Full Text:**

Available from *Free Access Content* in [Bangladesh Journal of Obstetrics and Gynecology](#)

---

**Title:** Alpha-methyldopa-induced acute hepatitis in pregnancy

**Citation:** Australian and New Zealand Journal of Obstetrics and Gynaecology, June 2006, vol./is. 46/3(256-257), 0004-8666;1479-828X (June 2006)

**Author(s):** Phadnis S.V., Sangay M.R., Sanusi F.A.

**Language:** English

**Publication Type:** Journal: Article

**Source:** EMBASE

**Full Text:**

Available from *Wiley* in [Australian and New Zealand Journal of Obstetrics and Gynaecology](#)  
Available from *Wiley* in [Australian and New Zealand Journal of Obstetrics and Gynaecology](#)  
Available from *Australian and New Zealand Journal of Obstetrics and Gynaecology* in [Patricia Bowen Library and Knowledge Service West Middlesex university Hospital](#)

---

**Title:** Centrally acting antihypertensive drugs. Present and future

**Citation:** Clinical and Experimental Hypertension, July 1999, vol./is. 21/5-6(859-873), 1064-1963 (July/August 1999)

**Author(s):** Van Zwieten P.A.

**Language:** English

**Abstract:** The classic centrally acting antihypertensives such as clonidine, guanfacine and alpha-methyl-DOPA (via its active metabolite alpha-methyl-noradrenaline) induce peripheral sympathoinhibition and a fall in blood pressure as a result of alpha<sub>2</sub>-adrenoceptor stimulation in the brain stem. These drugs have lost much of their clinical importance because of their unfavourable side-effects (sedation, dry mouth, impotence), which are also mediated by alpha<sub>2</sub>-adrenoceptors, although in other anatomical regions. Moxonidine and rilmenidine are the examples of a new class of centrally acting antihypertensives, which cause peripheral sympathoinhibition mediated by imidazoline (I<sub>1</sub>)-receptors in the rostral ventromedulla (RVLM). Their side-effect profile



appears to be better than that of clonidine and alpha- methyl-DOPA, probably because of a weaker affinity for alpha<sup>2</sup>-adrenoceptors. The mode of action, haemodynamic profile, antihypertensive efficacy and adverse reactions of the classic and newer centrally acting antihypertensives are the subject of the present survey.

**Publication Type:** Journal: Conference Paper

**Source:** EMBASE

---

**Title:** Acute reactive hepatitis in pregnancy induced by alpha-methyldopa.

**Citation:** Obstetrics and gynecology, Oct 1997, vol. 90, no. 4 Pt 2, p. 658-659, 0029-7844 (October 1997)

**Author(s):** Thomas, L A, Cardwell, M S

**Abstract:** Alpha-methyldopa is an antihypertensive medication used commonly in pregnancy. Reactive hepatitis is a severe, uncommon reported side effect of this medication. To our knowledge, there has been only one other reported case of alpha-methyldopa-induced hepatitis associated with pregnancy in the United States. A patient at 17 weeks' estimated gestational age was evaluated for elevated maternal serum alpha-fetoprotein, which is used generally as a screening test for birth defects. A thorough history, physical examination, and laboratory evaluation were performed, and alpha-methyldopa-induced maternal hepatitis was diagnosed. The astute clinician should include maternal hepatic dysfunction in the differential diagnosis of an elevated maternal serum alpha-fetoprotein and should consider obtaining aminotransferase levels after initiation of alpha-methyldopa therapy during pregnancy.

**Source:** Medline

**Full Text:**

Available from *Obstetrics and Gynecology* in [Patricia Bowen Library and Knowledge Service West Middlesex university Hospital](#)

Available from *Ovid* in [Obstetrics and Gynecology](#)

---

**Title:** Methyldopa hepatotoxicity in pregnancy: A case report

**Citation:** American Journal of Obstetrics and Gynecology, 1995, vol./is. 172/1(222-224), 0002-9378 (1995)

**Author(s):** Smith G.N., Piercy W.N.

**Language:** English

**Abstract:** A case of hepatotoxicity in a multiparous Native woman, who was begun on a regimen of methyldopa for control of chronic hypertension, is described. The patient was

first seen for clinical evidence of hepatotoxicity approximately 3 weeks after initiation of treatment. At presentation the aspartate aminotransferase level was 1800 IU/L and alanine aminotransferase was 2415 IU/L. There was also a significant prolongation of clotting time, which required therapy. Resolution of symptoms occurred after cessation of the medication. Although methyldopa is considered to have a wide margin of safety in the treatment of chronic hypertension in pregnancy, potentially serious adverse effects can occur. It is important to monitor serum aminotransferase levels after initiation of methyldopa therapy.

**Publication Type:** Journal: Article

**Source:** EMBASE

---

**Title:** Dose-response relationships with antihypertensive drugs.

**Citation:** Pharmacology & therapeutics, Jan 1992, vol. 55, no. 1, p. 53-93, 0163-7258 (1992)

**Author(s):** Johnston, G D

**Abstract:** A variety of antihypertensive drugs have been introduced into clinical practice at excessively high dose. Examples include most thiazide diuretics, propranolol, oxprenolol, atenolol, methyldopa, hydralazine and captopril. These very high doses have usually resulted from studies in which doses have been increased at regular intervals until the desired antihypertensive effect has been achieved or until unacceptable adverse effects have resulted. Frequently the starting doses were too high and the intervals between dose adjustment too short. In many cases these large doses resulted in unnecessary adverse effects--the adverse biochemical effects of thiazide diuretics, nephrotic syndrome, taste disturbances and neutropenia with captopril, the lupus syndrome with hydralazine and the central nervous system effects of methyldopa. Parallel group design with single doses and sufficient statistical power to distinguish between the upper and lower ends of the antihypertensive dose-response relationship should replace the dose-escalating design.

**Source:** Medline

---

**Title:** [Fatal toxic hepatitis in pregnancy. A discussion of the role of methyldopa].

**Citation:** Journal de gynécologie, obstétrique et biologie de la reproduction, Jan 1990, vol. 19, no. 2, p. 192-196, 0368-2315 (1990)

**Author(s):** Picaud, A, Walter, P, de Préville, G, Nicolas, P

**Abstract:** The authors report a case of toxic hepatitis in a woman of 22 years of age in the third trimester of her first pregnancy treated by methyldopa for hypertension of pregnancy which was diagnosed at 33 weeks of amenorrhoea. The prodromal symptoms were mild and consisted of nausea, vomiting and rise in temperature and this phase was associated with febrile jaundice without pruritus and it was only associated with coagulation disorders in the

third stage of labour. This was a case of mixed cytolytic hepatitis (ASAT x 3N) and cholestasis (x 1.5N). The outcome was fatal. The patient died three days after delivery following haematemesis and renal failure as well as hepatic encephalopathy. The main diagnostic feature was acute hepatic stasis in spite of the absence of pruritus and the presence of a raised temperature after hematolytic, viral and obstructive causes had been eliminated. Histology confirmed that there was toxic hepatitis. This aetiology was suggested by the timing of the symptoms after MD (methyldopa) had been taken. Elkington described methyldopa hepato-toxicity in 1969. Fatal cases in the literature were in patients who were over 40 years of age. Methyldopa is used in pregnant women because of its safety as far as the fetus is concerned. Mechanism by which it causes toxic hepatitis is a combination of abnormal metabolism (the cytochrome P450 chain produces an antigen) and an immune reaction in response to this antigen and these explain why such severe and potentially fatal forms of the condition exist.(ABSTRACT TRUNCATED AT 250 WORDS)

**Source:** Medline

---

**Title:** Adverse reactions to antihypertensive drugs in pregnancy

**Citation:** Obstetrical and Gynecological Survey, 1986, vol./is. 41/2(67-73), 0029-7828 (1986)

**Author(s):** Schoenfeld A., Segal J., Friedman S.

**Language:** English

**Publication Type:** Journal: Review

**Source:** EMBASE

---

**Title:** !a-Methyldopa and depression: A clinical study and review of the literature.

**Citation:** The American Journal of Psychiatry, May 1983, vol. 140, no. 5, p. 534-538, 0002-953X (May 1983)

**Author(s):** DeMuth, George W., Ackerman, Sigurd H.

**Abstract:** Among hypertensive patients, symptoms of depression were no more common in 42 Ss (mean age 61.9 yrs) treated with alphas-methyldopa than in 38 Ss (mean age 62.5 yrs) treated with other antihypertensive agents. As with other centrally active agents, alphas-methyldopa appeared to produce many behavioral symptoms, including mood changes, in predisposed individuals. Because alphas-methyldopa is a DOPA decarboxylase inhibitor but does not consistently affect mood or induce depression, its effects do not support a catecholamine hypothesis of depression. (43 ref) (PsycINFO Database Record (c) 2012 APA, all rights reserved)

**Source:** PsycInfo

**Full Text:**

Available from *Free Access Content* in [American Journal of Psychiatry](#)

**DISCLAIMER:** Results of database and or Internet searches are subject to the limitations of both the database(s) searched, and by your search request. It is the responsibility of the requestor to determine the accuracy, validity and interpretation of the results.

---