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REVIEW

Overview of clinical use and side effect profile of valsartan in Chinese hypertensive patients

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Abstract: We reviewed the Chinese and English literature for the efficacy and safety data of valsartan monotherapy or combination therapy in Chinese hypertensive patients. According to the data of ten randomized controlled trials, valsartan monotherapy was as efficacious as another angiotensin receptor blocker or other classes of antihypertensive drugs, excepting the slightly inferior diastolic blood pressure-lowering effect in comparison with calcium channel blockers. According to the data of six randomized controlled trials, valsartan combination, with hydrochlorothiazide, amlodipine, or nifedipine gastrointestinal therapeutic system, was more efficacious than monotherapy of valsartan, amlodipine, or nifedipine gastrointestinal therapeutic system. According to these trials, valsartan had an acceptable tolerability, regardless of whether it was used as monotherapy or in combination therapy. Nonetheless, several rare side effects have been reported, indicating that it should still be used with caution. This is of particular importance given that there are millions of hypertensive patients, worldwide, currently exposed to the drug.

Keywords: angiotensin receptor blocker, valsartan, hypertension, blood pressure, efficacy, side effect

Introduction

Since the first Chinese hypertension guidelines were published in 1999,[1] angiotensin receptor blocker (ARB) has been among the five classes of antihypertensive drugs recommended for the initiation and maintenance of antihypertensive therapy. Subsequent Chinese hypertensive guidelines, published in 2005[2] and 2011,[3] respectively, made similar recommendations for the choice of antihypertensive drugs. According to the 2012 Intercontinental Marketing Services report, valsartan, among several available agents in the class, is the most prescribed ARB for the management of hypertension in the People's Republic of China.[4] Valsartan is currently used as an agent of monotherapy or free-combination antihypertensive therapy and as a component of single-pill combination with hydrochlorothiazide or amlodipine as well.

In spite of its wide use in the People's Republic of China, valsartan has never been studied in any hard-outcome study in this country, except for the 33 Chinese patients enrolled in the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial.[5] Nonetheless, several randomized controlled trials were conducted to study blood pressure-lowering efficacy and safety of valsartan monotherapy versus other antihypertensive drugs[6–16] or combination therapy versus the component drugs.[17–21] In addition, several case reports on rare side effects have been published in the Chinese literature.[22–29]

In the present review, we first summarized the results of the comparative therapeutic studies that investigated efficacy and safety of valsartan monotherapy or combination

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antihypertensive therapy in Chinese hypertensive patients. For side effects profile, we additionally reviewed case reports.

Selection of studies

We searched randomized controlled trials and side effect case reports involving valsartan via PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) and VIP (http://www.cqvip.com/) for the English- and Chinese-language literature, respectively. For inclusion, a randomized controlled trial had to have been conducted in Chinese hypertensive patients and published in a peer-reviewed journal in the period from January 1, 1999 (from which time valsartan entered the Chinese market) to May 31, 2013; had a randomized parallel-group or cross-over design; compared valsartan monotherapy or combination therapy with placebo or other antihypertensive drugs; and assessed blood pressure at baseline and during follow-up. A case report must have been on a side effect attributable to the use of valsartan in the People's Republic of China and published in a peer-reviewed journal before May 31, 2013. We excluded trials in Chinese patients with a disease other than hypertension, such as heart failure or albuminuria.

Efficacy of valsartan monotherapy in Chinese hypertensive patients

We identified eleven trials that compared valsartan monotherapy with angiotensin-converting enzyme (ACE) inhibitors (benazepril[6] and enalapril[7,8]); another ARB (olmesartan[9,10]); calcium channel blockers ([CCBs] amlodipine,[11–13] benidipine,[14] and lacidipine[15]); or a diuretic (indapamide).[16] Table 1 shows the characteristics of these trials and the randomized patients. These trials had a sample size of 42 subjects[7] to 260 subjects,[11] and follow-up time of 1 week[15] to 48 weeks.[14] All these trials individually had insufficient power to show superiority, equivalence, or noninferiority at a difference of 2–3 mmHg systolic or diastolic blood pressure. Nonetheless, the pooled analyses were able to provide sufficient power for all trials (n=1,232)[6–16] as well as for the subgroup of trials that compared valsartan with CCBs (n=760),[11–15] but not for the subgroups of trials that compared valsartan with ACE inhibitors (n=201)[6–8] or another ARB (n=151).[9,10]

Overall, valsartan had similar blood pressure-lowering efficacy as the other classes of antihypertensive drugs or olmesartan, for systolic as well as diastolic blood pressure ($P \geq 0.18$) (Figure 1). There was significant heterogeneity across trials for diastolic blood pressure ($P \leq 0.001$) but not for systolic blood pressure ($P=0.99$). In drug-class-specific subgroup analyses, valsartan tended to be less efficacious than CCBs in reducing diastolic blood pressure (mean difference –2.41 mmHg; 95% confidence interval [CI]: –4.88 to 0.06 mmHg; $P=0.056$), with no significant heterogeneity across trials ($P=0.13$).[11–15]

Since the follow-up times of these trials varied substantially, and valsartan may require a few weeks or even months to exert its full antihypertensive effect, we performed subgroup analysis in the three trials that had a follow-up time of at least 24 weeks.[7,13,14] The results of this subgroup analysis were confirmatory: indeed, valsartan was similarly efficacious as enalapril in reducing systolic and diastolic blood pressure ($P \geq 0.73$), but tended to be less efficacious than CCBs in reducing diastolic (mean difference –3.52 mmHg; 95% CI: –7.01 to 0.01 mmHg; $P=0.051$) but not systolic blood pressure ($P=0.32$).

In addition, blood pressure-lowering efficacy of various classes of antihypertensive drugs, including valsartan, may be dependent on dietary sodium intake, which is known to be higher in northern than in southern People's Republic of China. We therefore performed subgroup analysis in trials conducted in northern[6,8,9,11,14] versus southern People's Republic of China.[7,10,12,13,15,16] The number of trials allowed comparison between northern and southern People's Republic of China for the treatment effects of all trials[6–16] and the trials of CCBs.[11–15] Valsartan was similarly efficacious as CCBs or all the other antihypertensive drugs in northern and southern People's Republic of China ($P \geq 0.19$), except that valsartan was significantly less efficacious in reducing diastolic blood pressure than CCBs (mean difference –4.86 mmHg; 95% CI: –7.53 to –2.19 mmHg; $P<0.001$) and all the other antihypertensive drugs (mean difference –2.50 mmHg; 95% CI: –4.59 to –0.40 mmHg; $P=0.02$) in southern People's Republic of China. However, the treatment effects between northern and southern People's Republic of China in reducing diastolic blood pressure differed significantly only in the trials of CCBs ($P=0.02$) but not all trials ($P=0.60$).

Efficacy of valsartan combination therapy in Chinese hypertensive patients

We identified six trials (Table 1) that compared valsartan single-pill (with hydrochlorothiazide[17,18] or amlodipine[19,20]) or free (with nifedipine gastrointestinal therapeutic system [GITS][21]) combination therapy with valsartan,[17–19,21] amlodipine,[19] or nifedipine GITS monotherapy.[20] All trials had a two-group parallel comparison, except one that compared the single-pill combination of valsartan and amlodipine with two different dosage groups of valsartan (80 and 160 mg/day).[19] These trials had a sample size of 123 subjects[18]

Table 1 Characteristics of controlled clinical trials that investigated the efficacy and safety of valsartan in Chinese hypertensive patients

Author	Year	Design	Location (People's Republic of China)	Subjects	Number of patients (Valsartan or valsartan combination/ Control)	Men (%)	Age (SD) (years)	SBP/DBP (SD) (mmHg) at baseline		Antihypertensive medication (mg/day)	Follow-up
								Valsartan	Control		
Valsartan monotherapy[a]											
vs ACEIs											
Zhang and Li[6]	2005	Open	Northern	EH	32/29	47.5	52 (9)	152 (10)/103 (6)	157 (10)/101 (6)	Valsartan 80–160 vs benazepril 10–20	8 weeks
Ko et al[7]	2005	DB	Southern	EH/DM	22/20	40.5	61 (11)	144 (20)/79 (8)	142 (13)/76 (11)	Valsartan 80–160 vs enalapril 5–10	1 year
Li and Zhang[8]	2007	Open	Northern	EH	49/49	89.8	NA	185 (14)/115 (12)	180 (16)/105 (15)	Valsartan 80–160 vs enalapril 10–20	8 weeks
vs ARBs											
Zhang et al[9]	2008	Open	Northern	EH	30/34	54.7	54 (6)	147 (10)/98 (10)	148 (9)/97 (10)	Valsartan 80–160 vs olmesartan 20–40	8 weeks
Li et al[10]	2009	Open	Southern	EH	44/43	83.0	47 (7)	154 (11)/95 (6)	154 (10)/95 (5)	Valsartan 80 vs olmesartan 20	8 weeks
vs CCBs											
Wang et al[11]	2002	Open	Northern	EH	130/130	100	46 (12)	167 (9)/102 (8)	168 (8)/101 (8)	Valsartan 80 vs amlodipine 5	8 weeks
Huang et al[12]	2007	Open	Southern	EH/elderly/AF	32/32	59.4	68 (6)	162 (9)/83 (11)	164 (8)/85 (11)	Valsartan 80–160 vs amlodipine 5–10	12 weeks
Cai et al[13]	2011	DB	Southern	EH/renal transplantation	75/75	58.0	37 (2)	147 (10)/87 (7)	149 (11)/87 (9)	Valsartan 80 vs amlodipine 5[b]	24 weeks
Peng et al (1)[14]	2010	Open	Northern	EH/proteinuria (protein <1 g/day)	57/59	50.9	43 (9)	149 (13)/97 (10)	150 (16)/96 (9)	Valsartan 80 vs benidipine 8	48 weeks
Peng et al (2)[15]	2010	Open	Northern	EH/proteinuria (protein 1–3 g/day)	61/59	52.5	43 (8)	150 (15)/95 (8)	151 (17)/95 (7)	Valsartan 80 vs benidipine 8	48 weeks
Liu et al[15]	2008	Open	Southern	EH	25/25	68.0	57 (9)	146 (15)/93 (13)	145 (11)/94 (17)	Valsartan 80 vs lacidipine 4	1 week
vs diuretics											
Yang et al[16]	2004	Open	Southern	EH	60/60	100	NA	148 (18)/97 (8)	148 (18)/98 (6)	Valsartan 80 vs indapamide 1.5	8 weeks
Valsartan combination[a]											
Valsartan/HCTZ combination											
Sun et al[17]	2007	DB	Multiple*	EH	419/423	58.2	52 (10)	143 (12)/96 (5)	144 (12)/96 (5)	Valsartan 80/HCTZ 12.5 vs valsartan 80	8 weeks
Zhang et al[18]	2008	DB	Northern	EH	61/62	56.3	55 (8)	151 (11)/99 (5)	148 (12)/98 (5)	Valsartan 80/HCTZ 12.5 vs valsartan 80	6 weeks
Valsartan/amlodipine combination											
Ke et al (1)[19]	2009	DB	Multiple*	EH	274/273/267	62.9	54 (9)	142 (13)/95 (5)	142 (13)/95 (5) 139 (12)/95 (5)	Valsartan 80/amlodipine 5 vs valsartan 80 vs valsartan 160	8 weeks
Ke et al (2)[19]	2009	DB	Multiple*	EH	290/290	61.7	51 (10)	141 (12)/73 (8)	140 (11)/74 (8)	Valsartan 80/amlodipine 5 vs amlodipine 5	8 weeks
Wang et al[20]	2013	Open	Multiple*	EH	272/268	50.0	54 (9)	147 (7)/87 (8)	146 (7)/87 (8)	Valsartan 80/amlodipine 5 vs nifedipine GITS 30	12 weeks
Valsartan/nifedipine GITS combination											
Ke et al (3)[21]	2012	Open	Multiple*	EH/Asian	177/182	52.4	56 (10)	152 (8)/94 (7)	152 (8)/94 (7)	Valsartan 80/nifedipine GITS 30 vs valsartan 160	12 weeks

Notes: [a]The valsartan monotherapy trials are listed in the order of comparison drug class, the drug, and the year of publication,[6–16] and the valsartan combination therapy trials are listed in the order of the combination drug and the year of publication;[17–21] [b]at the end of 4-week monotherapy, 25 metoprolol per day was added if blood pressure was not controlled to a level below 130/80 mmHg.[13] *Multiple, multi-center studies across southern and northern People's Republic of China.

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARBs, angiotensin receptor blockers; DB, double-blind; DBP, diastolic blood pressure; DM, diabetes mellitus; EH, essential hypertension; GITS, gastrointestinal therapeutic system; HCTZ, hydrochlorothiazide; NA, not available; SBP, systolic blood pressure; SD, standard deviation; vs, versus.

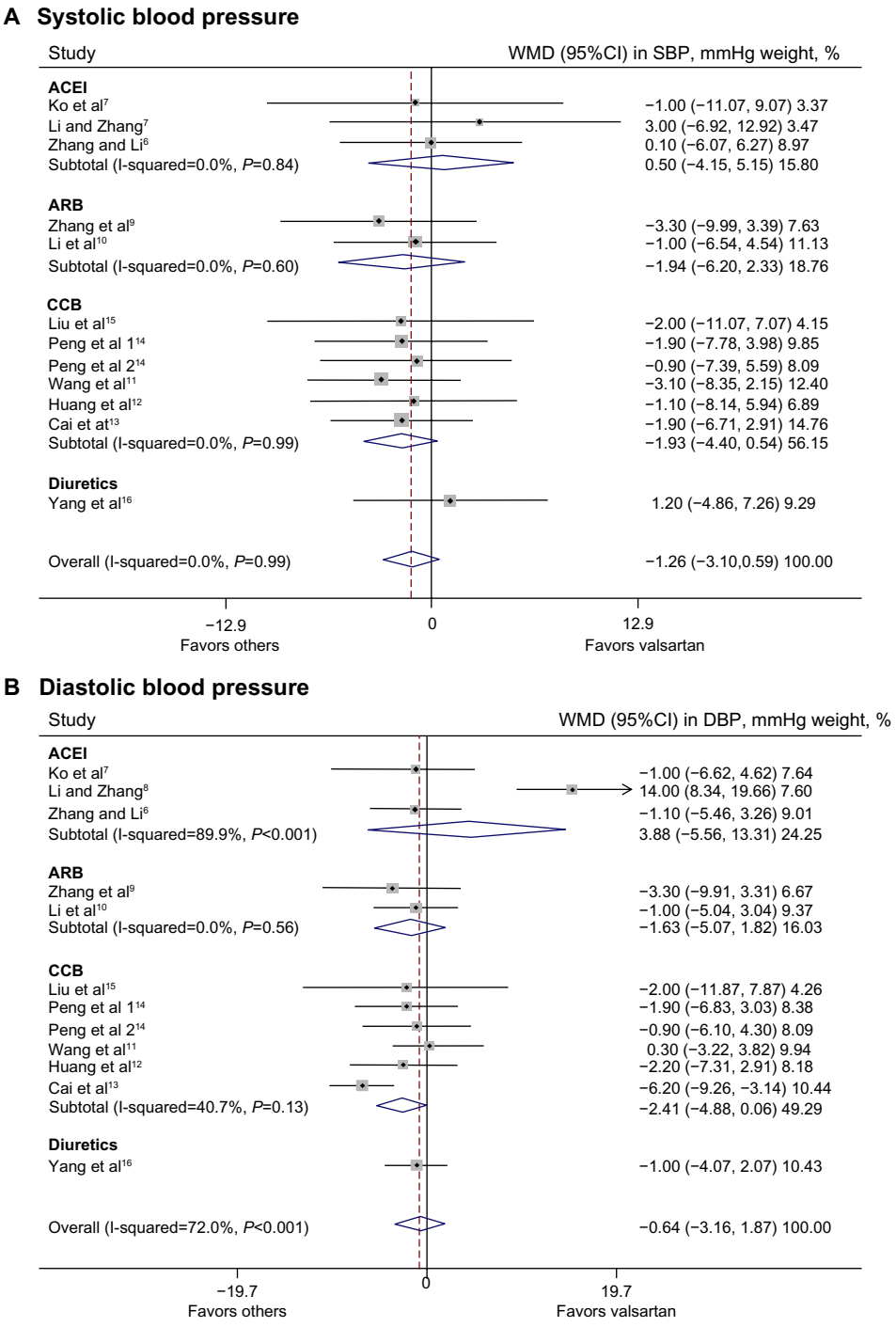

Figure 1 SBP (**A**) and DBP (**B**)-lowering efficacy of valsartan monotherapy versus other classes of antihypertensive drug.
Notes: Squares indicate WMD in trials, with a size proportional to the number of patients. 95% CIs for individual trials are denoted by lines and those for the pooled mean differences by diamonds.
Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; SBP, systolic blood pressure; WMD, weighted mean difference.

to 842 subjects[17] and follow-up time of 6 weeks[18] to 12 weeks.[20,21] All but two[18,21] of these trials individually had sufficient power to show superiority of valsartan combination against valsartan or amlodipine monotherapy at a difference of 2–3 mmHg systolic or diastolic blood pressure. Accordingly, all but the two inadequately powered[18,21] trials showed significantly larger reductions in both systolic and diastolic blood pressure in patients on valsartan combination than those on monotherapy with valsartan or amlodipine.

Overall, valsartan combination, on average, showed reduced systolic and diastolic blood pressures 2–6 mmHg more than monotherapy (Figure 2). If the superiority in blood

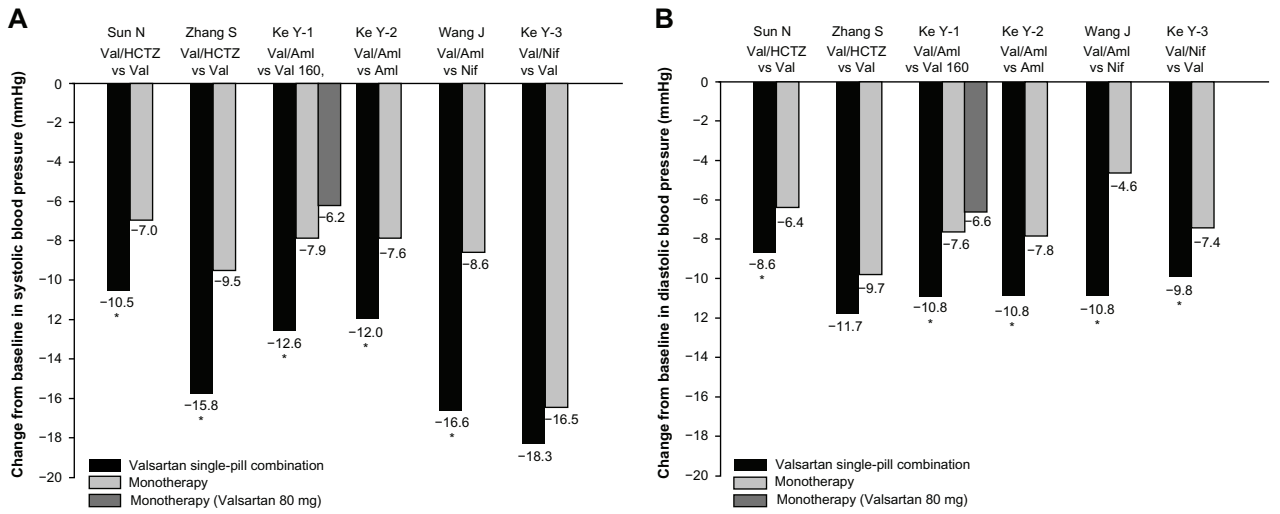

Figure 2 Systolic and diastolic blood pressure reductions in the combination therapy and monotherapy groups.
Note: *$P<0.05$ vs monotherapy.
Abbreviations: Aml, amlodipine; HCTZ, hydrochlorothiazide; Nif, nifedipine gastrointestinal therapeutic system; Val, valsartan; Val 80, Val 80 mg; Val 160, Val 160 mg; vs, versus.

pressure-lowering efficacy was represented by the percentage of patients who achieved the blood pressure goal as defined in each trial, the improvement in the valsartan combination therapy group, compared with valsartan, amlodipine, or nifedipine GITS, was statistically significant in all trials ($P<0.001$), with an absolute percentage change of 10%[17] to 25%.[19]

In one trial that compared valsartan 80 mg/amlodipine 5 mg/day with amlodipine 5 mg/day, ambulatory blood pressure monitoring was performed in 82 of the 590 randomized subjects.[19] In this particular sub-study, ambulatory blood pressure differences in favor of the valsartan/amlodipine combination (mean systolic/diastolic blood pressure difference −7.1/−6.6 mmHg, −7.2/−6.8 mmHg, and −6.3/−6.0 mmHg during the whole day, daytime and nighttime, respectively) were much larger than those observed by clinic blood pressure measurement in the total study population (−4.4/−3.0 mmHg, mean systolic/diastolic blood pressure difference, respectively). These interesting observations warrant further investigation.

Side effects profile in randomized controlled clinical trials

In some,[6–11,17–21] though not all,[12–16] of the aforementioned randomized controlled trials, information on adverse events and serious adverse events was systematically collected and reported (Table 2). In the monotherapy trials,[6–11] the incidence rate of adverse events with valsartan was lower than with ACE inhibitors (pooled odds ratio associated with ACE inhibition 3.51; 95% CI: 1.45–9.25; $P=0.0035$)[6–8] and similar to the rate with another ARB ($P=0.80$)[9,10] and amlodipine ($P=0.99$).[11] There was no adverse event that was typically overrepresented in the valsartan group, regardless of the follow-up time.

In the combination therapy trials,[17–21] the incidence rate of drug-related adverse events was higher with valsartan/hydrochlorothiazide combination than with valsartan monotherapy (pooled odds ratio associated with the combination 1.71; 95% CI: 1.05–2.82; $P=0.029$)[17,18] and lower with valsartan/amlodipine combination (5.7%) than with nifedipine GITS (15.6%; odds ratio associated with nifedipine GITS 3.07; 95% CI: 1.65–5.99; $P<0.001$).[20] However, the incidence rate of the drug-related adverse events was similar between valsartan/amlodipine combination and valsartan or amlodipine monotherapy ($P\geq0.59$)[19] and between valsartan/nifedipine GITS combination and valsartan monotherapy ($P=0.99$).[21] The adverse events reported in the combination groups to a large extent reflected a component of the combination other than valsartan, such as hyperuricemia and hypokalemia associated with hydrochlorothiazide,[17] palpitations and flushing associated with nifedipine GITS,[21] and peripheral edema associated with amlodipine[19,20] and nifedipine GITS.[21]

In addition, one randomized study specifically investigated the hematologic effect of valsartan (n=30) versus benazepril (n=30).[22] In this study, valsartan significantly ($P<0.001$) decreased serum concentrations of erythropoietin (mean ± standard deviation from 14.2±3.2 to 12.1±2.9 U/L) and hemoglobin from baseline (from 144.3±13.8 to 135.2±14.8 g/L), whereas these hematologic measurements did not change with benazepril ($P>0.05$). This observation also warrants further investigation.

Table 2 Side effect profile in controlled clinical trials that compared valsartan with other antihypertensive drugs

Author	Incidence rate of adverse events, (% number of events/ subjects)[a]		Most frequently reported adverse events (number of patients)	
	Valsartan	Other drugs	Valsartan	Other drugs
Valsartan monotherapy				
vs ACEIs				
Zhang and Li[6]	12.5 (4/32)	15.6 (5/29)	Weakness (2) Dizziness (1) Dry mouth (1)	Cough (3) Dizziness (1) Tinnitus (1)
Ko et al[7]	13.6 (3/22)	45.0 (9/20)	Numbness (1) Joint pain (1)	Cough (7) Palpitations (1) Minor stroke (1)
Li and Zhang[8]	4.1 (2/49)	20.4 (10/49)	Headache (1) Dry mouth (1)	Cough (5) Headache (3) Tinnitus (1)
vs ARBs				
Zhang et al[9]	6.7 (2/30)	8.8 (3/34)	Dizziness (1) Weakness (1)	Dizziness (2) Weakness (1)
Li et al[10]	2.3 (1/44)	4.7 (2/43)	Headache (1)	Cough (1) Headache (1)
vs CCBs				
Wang et al[11]	1.5 (2/130)	1.5 (2/130)	Cough (1) Dizziness (1)	Edema (1) Headache (1)
	Combination	**Monotherapy**	**Combination**	**Monotherapy**
Valsartan combination therapy				
Valsartan/hydrochlorothiazide				
Sun et al[17]	8.9 (38/429)	5.1 (22/435)	Hyperuricemia (8) Dizziness (7) Hypokalemia (4)	Dizziness (8) Headache (3) Hypokalemia and abnormal liver function (2)
Zhang et al[18,b]	21.0 (13/62)	15.6 (10/64)	Headache Dizziness Chest distress	Headache Dizziness Chest distress
Valsartan/amlodipine				
Ke et al (1)[19,c]	4.4 (12/274)	4.4 (12/274)/ 4.9 (13/268)	Edema (4) Dizziness (3)	Edema (2) Dizziness (1)/ Dizziness (4) Edema (1)
Ke et al (2)[19,c]	10.7 (31/291)	9.0 (26/290)	Abnormal liver function (7) Dyslipidemia (6) Dizziness (3)	Abnormal liver function (4) Dizziness (3) Dyslipidemia (2)
Wang et al[20]	5.7 (16/282)	15.6 (44/282)	Headache (3) Edema (2) Dizziness (1)	Headache (13) Palpitations (11) Edema (7)
Valsartan/nifedipine GITS				
Ke et al (3)[21]	4.5 (8/177)	4.4 (8/182)	Peripheral edema (1) Flushing (1) Palpitation (1)	Dizziness (2) Headache (1)

Notes: [a]The incidence rate was reported for withdrawals in the trial of Li W et al[10] and for drug-related adverse events in all the combination therapy trials;[17–21] [b]the number of patients was not reported;[18] [c]there were two control groups with two different dosages of valsartan monotherapy (80 and 160 mg/day).

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CCBs, calcium channel blockers; GITS, gastrointestinal therapeutic system; vs, versus.

Side effects profile in clinical practice

Because of the limited number of patients in a randomized controlled trial, rare side effects are usually difficult to detect; however, in clinical practice, with millions of users of a drug, rare side effects can be discovered. We reviewed case reports that described side effects probably or possibly related to the use of valsartan, and identified eight publications (Table 3).[23–30] There was one case in each of these eight reports. Of these eight cases, seven had a single clinical manifestation (angioedema, cough, drug eruption, hematuria, hypotension, muscle pain, or urticaria), and one had multiple clinical manifestations (urticaria, vertigo, muscle pain, and upper respiratory tract infection). Angioedema, drug eruption, and urticaria can be similarly attributable to hypersensitivity to valsartan.

Table 3 Side effect profile of valsartan in case or case series reports in the therapeutic management of hypertension in the People's Republic of China

Author	Year	Side effects[a]	Number of patients	Age (years)	Sex
Huang et al[23]	2004	Hypotension	1	62	Male
Li et al[24]	2004	Angioedema	1	65	Male
Li et al[25]	2006	Muscle pain	1	69	Female
Zhang[26]	2008	Cough	1	80	Male
Jiao[27]	2008	Urticaria, vertigo, muscle pain, and upper respiratory tract infection	1	63	Female
Xu[28]	2009	Hematuria	1	60	Female
Hua and Zhou[29]	2011	Urticaria	1	62	Male
Zhuang[30]	2012	Drug eruption	1	50	Male

Notes: [a]the side effects in all reports disappeared after the drug was discontinued.

Conclusion

Valsartan monotherapy was as efficacious as any another ARB or other classes of antihypertensive drugs, except in the case of the slightly inferior diastolic blood pressure-lowering effect in comparison with CCBs. However, valsartan combination therapy, either with amlodipine, hydrochlorothiazide, or nifedipine GITS was more efficacious than monotherapy of amlodipine or valsartan. Valsartan had acceptable tolerability, regardless of whether it was used as monotherapy or in combination therapy. Nonetheless, several rare side effects have been reported, indicating that valsartan should still be used with caution. This point is of particular importance given the millions of hypertensive patients currently exposed to the drug. In addition, all trials included in the present review were conducted exclusively or predominantly in ethnic Han Chinese. More research is required in ethnic minority Chinese populations, especially those with different lifestyle.

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